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Original article

Determinants of home parenteral nutrition dependence and survival of 268 patients with non-malignant short bowel syndrome

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SUMMARY

Background & aims: Short bowel syndrome (SBS) is a rare and severe condition where home parenteral nutrition (HPN) dependence can be either permanent or transient. The timing of HPN discontinuation and the survival, according to SBS characteristics, need to be further reported to help plan pre-emptive intestinal transplantation and reconstructive surgery.
Methods: 268 Non-malignant SBS patients have been followed in our institution since 1980. HPN dependence and survival rate were studied with univariate and multivariate analysis.
Results: Median follow-up was 4.4 (0.3–24) years. Actuarial HPN dependence probabilities were 74%, 64% and 48% at 1, 2 and 5 years, respectively. In multivariate analysis, HPN dependence was significantly decreased with an early (<6 mo) plasma citrulline concentration >20 μmol/l, a remaining colon >57% (4/7) and a remnant small bowel length >75 cm. Among the 124 patients who became HPN independent, 26.5% did so more than 2 years after SBS constitution.
Conclusions: This study indicates that long-term HPN is required in 47% of SBS patients started on this therapy. HPN independence is significantly associated with the remnant small bowel length, remaining colon and early plasma citrulline concentration. Noteworthy, HPN dependence could be reversed until 5 years after SBS constitution.

1. Introduction

Intestinal failure (IF) is a highly disabling condition characterized by the inability to maintain protein-energy, fluid, electrolyte and micronutrient balances under a normal unrestricted diet.[1] IF ultimately leads to increasing malnutrition and even death if not circumvented by home parenteral nutrition (HPN).[2] In adult patients, short bowel syndrome (SBS) is the major cause of IF.[3]

In SBS, HPN dependence may be either permanent (or deemed irreversible) or transient.[4] Although it is still debated, the human intestine has an inherent ability to adapt functionally and morphologically after a massive resection, leading to an improvement in its absorptive capacity overtime.[4] These changes are mainly related to increased intraluminal absorption and enteral neuro-hormonal stimuli but also to behavioural changes, mainly spontaneous oral hyperalimentation (adaptive hyperphagia).[5] All these changes aim to ultimately discontinue HPN. Classically, it is accepted that the time to discontinue HPN may be of at least 2 years in adult patients with a colon in continuity.[6] However, late HPN discontinuation has also been described.[7,8] Therefore, the timing of HPN discontinuation, according to the characteristics of the patients and SBS, needs to be further investigated.

HPN has become the standard treatment for IF, offering a long-term survival demonstrated by several studies.[6,9,10] Unfortunately, HPN is associated with complications, including progressive steatohepatitis and further liver failure, catheter-related complications and the inability to cope with the HPN regimen.[11] Intestinal transplantation (ITx) is also an alternative therapy for patients with permanent and irreversible HPN dependence.[12] However, despite its relative safety and efficacy, ITx survival still appears to be lower than with HPN.[6,12–14] Consequently, based on the American Society of Transplantation as well as Medicare and Medicaid, ITx should be considered in patients with permanent HPN dependence and in cases of failure of HPN, high risk of death, severe SBS, frequent hospitalizations and the unwillingness of the patients to accept long-term HPN.[12] Recently, a European study supporting the choice

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of HPN showed that the survival of the patients who fulfilled the criteria for ITx without HPN-related complications was similar to the survival of the patients who did not fulfil the criteria for ITx.[14]

Herein, we report a large series of adult SBS patients over a 25-year period of follow-up to better define these two important clues in the management of SBS patients on HPN: (1) HPN dependence and (2) long-term survival of SBS patients on HPN.

2. Patients and methods

2.1. Patients

From January 1980 to April 2006, all consecutive adult patients with a short bowel syndrome (remnant small bowel length of ≤150 cm) that have required HPN in our institution, an approved centre for IF and HPN, were included in a retrospective cohort study. Patients were recruited from our personal HPN database and/or a standardized hospital inpatient dataset diagnosis. We excluded the patients with evolving primary malignancies present within the first year of the follow-up ($n = 8$), patients who had received treatments other than HPN for intestinal failure, e.g., recombinant human growth hormone or teduglutide and the patients that have discontinued HPN within 3 months ($n = 21$). We included patients who had reconstructive surgery of the remnant small bowel (segmental reversal small bowel was performed in 28 cases). Eighty patients from this series have already been included in a previous study and 30 in the Pironi's study.[6,14] This work has been approved by the local ethical committee according to French law. The data records included the demographic data of the patients, aetiology of SBS, characteristics of past surgical procedures, characteristics of intestinal tract, HPN dependence and patient mortality including the causes of death. The remnant small bowel was evaluated on the basis of operative records and expressed as a length. The remaining colon was evaluated according to the method of Cummings et al.[15] Briefly, the length of the colon was divided into seven sections, each part thus represents 14% of the colon. These divisions correspond approximately to the sites at which jejunocolonic anastomosis were made. The length of remaining colon was expressed as a percentage. SBS was classified as type 1 (jejunostomy), type 2 (jejunocolonic anastomosis), or type 3 (jejuno-ileocolonic anastomosis). Special attention was focused on the presence (or absence) of chronic intestinal obstruction, either functional or mechanical.[16] The routine parameters collected for nutritional evaluation included weight, height, BMI and resting energy expenditure according to the Harris and Benedict equation.[17] Plasma amino acid sampling were performed after a overnight fast, as described previously, in order to determine the post-absorptive plasma citrulline concentration.[18] Post-absorptive plasma citrulline concentration was determined under stable conditions in absence of overt dehydration, early, between 1 and 6 months after SBS constitution and after at least a 2-year adaptive period following re-establishment of digestive continuity.

2.2. HPN management

The conditions under which HPN was administered have been outlined elsewhere.[6,19] The dietary program was composed of unrestricted free solid food ingestion and, especially in patients with end-enterostomy, the use of either oral rehydration solution or mineral Vichy-St-Yorre and tap water restriction. All patients were educated by trained dietetician to promote spontaneous oral hyperphagia. The composition and volume of solutions given to the patients and the number of infusions per week were adjusted to individual needs. The attempt was always made to set up at a minimum the level of HPN regimen program according to the nutritional balance monitoring as previously described.[6,19] HPN characteristics regarding the composition, volume and frequency of the infusions were collected at the end of the follow-up. The degree of HPN requirement was calculated as the percentage of the daily mean of total parenteral energy infused divided by 1.5 times the resting energy expenditure.[5,20]

2.3. Absorption study

SBS patients underwent a metabolic study to evaluate the intestinal macronutrient absorption at various times during the course of their HPN.[5,20] Briefly, over a 6-day period, the first 3-day equilibrium period was used to confirm that patients were continuing their spontaneous intake of energy, carbohydrates, lipids, proteins, and fibres, while absorption was measured the last 3 days. Unrestricted intake was measured by trained dietetician (food diary) by amount or weight and calculated with Bilnut software (Bourgerette P, Rolshansen M; BILNUT 4.0; SCDA Nutrisoft, Cerelles, France). Stool was collected daily and frozen at −20 °C. Protein, lipid, and total energy were determined by nitrogen elemental analysis (N analyser Flash EA1112; Thermo Scientific, Waltham, MA, the method of Van de Kamer and bomb calorimetry, PARR 1351 bomb calorimeter; Parr Instrument, Moline, IL). Quantification of carbohydrate-derived energy was calculated by subtracting the energy associated with the protein and lipid components from the total energy. The calorie-conversion factors used were 4.2, 9.35, and 5.65 kcal/g for carbohydrates, lipids, and proteins, respectively. The coefficient of net intestinal absorption represented the proportion of ingested energy not recovered in the stool output. The degree of nutritional oral autonomy was calculated as the total calories ingested daily multiplied by the net total caloric absorbed fraction and divided by 1.5 times the resting energy expenditure.[5,20]

2.4. Statistical analysis

All patients were followed-up until death or June 2006 when the data were collected. HPN duration was calculated from the date of HPN start, up to the death, definitive HPN cessation, or end of the follow-up. HPN dependence was defined as unability of patients to be definitively weaned off HPN at the time of data collection. The survival time was calculated from the date of HPN start to the death or end of the follow-up. For statistical analysis of survival, patients who have undergone ITx were presumed dead at the time of the transplantation. HPN dependence and survival probabilities were calculated using the Kaplan–Meier method. HPN dependence and survival variables were compared using univariate and multivariate analyses. HPN dependence and survival distributions were compared using the log rank test, with p values of 0.05 considered statistically significant, according to the concomitant variables of survival and HPN dependence. Qualitative categories of values were defined by dichotomy from median value in two distinct groups of equal size. To identify the independent factors contributing to HPN dependence and survival, Cox proportional hazard models were then adjusted to the above-mentioned variables with an ascending stepwise procedure using SPSS statistical software (SPSS Inc, Chicago, Illinois). Quantitative variables were expressed as medians (ranges) or as means ± standard deviation; both probabilities of survival and Hazard risks (RRs) were provided with 95% confidence intervals (CIs). Spearman's two-tailed test was used to assess correlations. To determine early and postadaptive plasma citrulline concentrations performance, receiver operating characteristic (ROC) curves were constructed and area under curves (AUROCs) calculated with an empirical non parametric method. The characteristics of the patients at different time points were compared by