Zuzanna Zaczek

Optimization of nutrition and acceleration of intestinal rehabilitation in patients with short bowel syndrome, with special reference to end jejunostomy syndrome

Abstract

Introduction

Short bowel syndrome (SBS) is a condition resulting from extensive resection, congenital abnormality in the structure or dysfunction of the small intestine, leading to deterioration in water and nutrient absorption and subsequently malnutrition, dehydration, and even death. SBS is a form of intestinal failure (IF). There are three types of SBS, of which the type associated with the highest risk of malnutrition and complete dependence on parenteral nutrition (PN) is end jejunostomy, which is characterized by excessive stomal output that increases after ingestion of solid food and fluid.

In the course of short bowel syndrome, the adaptation phase, which lasts up to 2 years after resection, plays an extremely important role. It is estimated that intestinal failure reverses in 50% of patients during the adaptation phase. In other cases, intestinal failure becomes a chronic condition requiring long-term intravenous nutrition. Nowadays, this therapy can be performed at home. Stimulation of the intestinal mucosa by the presence of food in its lumen has a positive effect on acceleration of the intestinal adaptation process, as do pharmacological methods, of which the effect of the analog of glucagon-like peptide 2 (GLP-2) - teduglutide (TED) - is the best documented.

Nutrition has a significant impact on the health of patients with short bowel syndrome, especially end jejunostomy syndrome, and improper nutritional management can lead to deterioration of their health status. Parenteral nutrition (PN) is currently a standard of care, but this method carries the risk of metabolic, organic, and septic complications. Therefore, solutions that can increase oral intake and decrease the need for parenteral nutrition are being sought.

This dissertation, which represents a thematically related series of publications with a total Impact Factor value of 11,592 and a number of ministerial points: 280, consists of three original papers.

Aim

The aim of this dissertation was to study the influence of selected variables on the optimization of nutrition and the process of intestinal rehabilitation in patients with short bowel syndrome, with special reference to end jejunostomy syndrome.

Specific aims

Publication I

The aim of the study was to compare the outcomes of two nutritional approaches: unrestricted and restricted oral intake in patients with short bowel syndrome and end jejunostomy receiving HPN in relation to liver and kidney biochemical markers and time to reconstructive bowel surgery with correlation to stoma output.

Publication II

The second aim was to evaluate the effects of thickening powders on reducing stoma output in individuals with short bowel syndrome and high-output end jejunostomy, and thus their potential use in the nutritional management of these patients.

Publication III

The aim of the third study was to evaluate changes in parenteral nutrition orders and BMI in HPN patients with SBS during a 9-year follow-up period after they stopped taking teduglutide.

Materials and Methods

Publication I

The study group consisted of 20 new patients with short bowel syndrome and high output end jejunostomy who were enrolled in a HPN procedure. Once stabilised, patients were divided into two equal groups according to their preferences. Patients in group A (n = 10) had their oral nutrition restricted to keep the volume of stoma excretion below 1000 ml/day, whereas

patients in group B (n = 10) had no restrictions on oral nutrition. All patients received complete parenteral nutrition tailored to their individual needs, which they continued at home after qualification was completed. At follow-up visits conducted within 6 months of discharge, the volume of stomal output, degree of diuresis, and presence of symptoms affecting quality of life (QOL) were assessed, blood tests were performed, and, if necessary, the composition of the nutritional mixture was adjusted to the patient's current needs. Retrospective analysis of data collected at the visits included information on the timing of surgical reconstruction of the gastrointestinal tract and the number of hospitalizations during the follow-up period, as well as blood bilirubin and creatinine levels after 6 months of home parenteral nutrition, stoma discharge volume, and subjective assessment of patients' quality of life.

Statistical analysis was performed using STATISCTICA 13.3 software (TIBCO Software Inc, Palo Alto, California, USA). Basic descriptive analyzes were performed. Differences between groups with respect to individual parameters were assessed using the nonparametric Mann-Whitney U test. Effect size for observed differences was estimated using the Cohen's d factor, with 0.2 representing a "small," 0.5 a "medium," and 0.8 a "large" effect size. Null hypothesis testing was performed for each analysis with the a priori assumption of statistical significance at 0.0125.

Publication II

The study included 16 adult patients with short bowel syndrome and high-output end jejunostomy who received fluids thickened with a thickening powder during hospitalization in the Department of General Surgery and Clinical Nutrition. During hospitalization, all subjects received TPN tailored to their needs. In the first phase of the study, which lasted 4 days, patients received 600 ml of room-temperature water per day, divided into 3 200-ml portions. In the next 4 days (phase II), patients received the same amount of water (600 ml per day) with an addition of thickening powder consisting of maltodextrin, xanthan gum, and guar gum. The solution was prepared according to the manufacturer's instructions by adding 2 scoops of the product per 200 ml of water until a slightly thick consistency - level 2 according to the *International Dysphagia Diet Standardization Initiative* (IDDSI) guidelines - was achieved. The daily volume of excretion from the stoma was measured on all study days, and patients were asked to subjectively rate the consistency of excretion. The collected data were analyzed retrospectively, taking into account the following information: Height and weight, diagnosis associated with the occurrence of SBS, and daily volume of stomal output on each study day.

Statistical analysis was performed using STATISCTICA 13.3 software (TIBCO Software Inc., Palo Alto, California, USA). Basic descriptive analyzes were performed. Cross-tabulations and the Fisher-Freeman-Halton exact test were used to assess differences between categorical variables, whereas the Mann-Whitney U test with continuity correction was used to analyze differences between men and women. The volumes of stomal output after ingestion of water and the mixture of water and thickener were compared using the Wilcoxon signed-rank test with the effect size coefficient eta-squared.

Publication III

In this multicenter study, we performed a retrospective analysis of prospectively collected medical records of adult patients with parenteral nutrition-dependent short bowel syndrome during a 9-year follow-up period after completion of treatment with teduglutide. The study group consisted of 13 HPN patients with short bowel syndrome who were treated with TED in randomized clinical trials between 2009 and 2013 and still required parenteral nutrition 9 years after completion of therapy. Patients who died or were weaned from HPN during the follow-up period were excluded from the analysis. Data were documented and collected prospectively throughout the follow-up period at mandatory quarterly visits to home parenteral nutrition centers. The retrospective data analysis, conducted in December 2021, considered patient weight and height; parenteral nutrition orders, including volume, energy value, and amino acid content of the nutritional mixture; SBS-associated diagnosis and type of SBS; date of HPN initiation and clinical trial initiation, and duration of teduglutide administration. BMI values were calculated by dividing body weight [kg] by height [cm] squared. The above parameters were examined at 7 time points: before initiation (T_0) and immediately after discontinuation of teduglutide (T_{end}), then 12, 24, 60, 84, and 108 months (1, 2, 5, 7, and 9 years) after cessation of therapy.

Statistical analysis was performed using STATISCTICA 13.3 software (TIBCO Software Inc., Palo Alto, California, USA). Basic descriptive analyzes were performed. The Mann-Whitney U test with continuity correction was used to test the null hypothesis for the independent variables, while the Wilcoxon rank test or the Friedman test with the Dunn-Sidàk post hoc test was used for the dependent variables. The level of $p < 0.05$ was considered statistically significant.

Results

Publication I

Daily stomal output volumes in the group of patients who restricted their oral intake decreased by an average of 1950 ml within 4 weeks after discharge, whereas the other group had an average increase in secretion of 100 ml. Restriction of oral feeding was associated with a reduction in time to surgical restoration of gastrointestinal continuity ($p = 0.004$) and fewer hospitalizations before surgery ($p = 0.035$) compared with patients without restrictions. Statistically significant lower concentrations of bilirubin ($p = 0.019$) and creatinine ($p < 0.01$) in blood plasma were observed 6 months after the start of HPN in the group that restricted oral intake. In addition, a deterioration in QOL was observed in patients fed ad libitum due to sleep disturbances related to the need to empty the bag at night.

Publication II

A significant reduction in stoma output volume was observed after administration of water mixed with thickening powder compared with drinking plain water without any additives (550 ml vs. 811.9 ml; $z = 3.154$, $p = 0.002$). Differences in volumes of end jejunostomy discharge were observed when comparing 4-day mean values for stages as well as median values between particular days. In addition, 93.75% of patients reported significantly thicker consistency of jejunal contents in the second stage of the study, resulting in a reduction in the frequency of stoma bag emptying compared with the first four days.

Publication III

Body weight values (expressed by BMI) varied considerably between the time points studied, but significant differences compared with T_{end} were not observed until 60 and 84 months (5 and 7 years) after the end of treatment with TED. Compared with pretreatment values, no significant differences in body mass were observed at any of the time points studied. Weekly volumes of parenteral nutritional differed significantly between all observation time points ($\chi 2 = 34.860$, $p < 0.001$). The study showed that 69.3% of patients required an increase in PN volume within 12 months after discontinuation of the drug, but at this time point, the volumes remained statistically significantly lower than before initiation of therapy ($p = 0.027$). At 5 years after the end of treatment, the need for PN volume in the study group was statistically significantly higher than at the end of treatment ($p = 0.036$), but was not significantly different from the value before the start of treatment. After 7 years, almost 85% of patients received nutritional admixtures with a volume 64.01% (median) greater than at the time of

discontinuation of TED, and the difference in results compared to the values obtained after the end of treatment was statistically significant (p = 0.007). At this stage, the volume of intravenous nutrition exceeded the pretreatment value in 4 patients (30.8%). At 9 years after teduglutide discontinuation, weekly parenteral nutrition volume had increased in 92.3% (n = 12) of study participants compared with the time of drug discontinuation. At this time, parenteral nutrition volume was 0.56 - 44.84% (median 21.21%) greater than before teduglutide administration in nearly 54% of patients. In the remaining patients, the volume was 26.19% lower compared with baseline. Statistically significant differences were observed in weekly energy ($\chi2$ = 34.39936, p < 0.001) and amino acid ($\chi2$ = 22.67442, p < 0.001) content in parenteral admixture between time points. At no time point did the intake of these two components differ significantly from the value before the start of treatment. A statistically significant increase in PN energy content was observed 5, 7, and 9 years after the end of treatment (p values: 0.012; 0.02, < 0.001, respectively).

Conclusions

Publication I

Unrestricted oral intake of foods and fluids in patients with end jejunostomy syndrome is associated with increased stomal output, leading to excessive losses of essential compounds, which may subsequently lead to deterioration of liver and kidney function, among other complications. Restricting oral intake may be an effective means of reducing the risk of complications associated with long-term parenteral nutrition and shortening the time to surgical reconstruction of the gastrointestinal tract.

Publication II

Thickening fluids with thickening powders, commonly used to facilitate swallowing in patients with dysphagia, appears to have a beneficial effect on reducing the daily volume of jejunal contents and improving its consistency, thereby reducing the risk of nephrologic complications associated with long-term parenteral nutrition. The results suggest that the use of thickening powder may be beneficial in the nutritional management of patients with high-output end jejunostomy.

Publication III

After discontinuation of teduglutide, anthropometric indicators change over time and the parenteral nutrition programme must be adjusted. After an initial increase in the first year after

drug discontinuation, PN volume requirements remain relatively stable for approximately 4 years and then increase again significantly 5-9 years after teduglutide discontinuation. In some patients, parenteral nutrition volume may exceed pre-teduglutide levels over time. It is extremely important to carefully monitor patients who have discontinued therapy with this drug.