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Effect of growth hormone, glutamine, and enteral nutrition on intestinal adaptation in patients with short bowel syndrome

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Background/aims: *In the management of short bowel syndrome, the benefits of treatment with growth hormone, glutamine, and enteral nutrition for intestinal adaptation is still controversial. The aim of the current study was to determine whether growth hormone, glutamine, and enteral nutrition had positive effect on intestinal adaptation.* ***Materials and Method:*** *Twelve patients with short bowel syndrome (small-bowel remnant length, 59±9 cm; mean±SEM) received growth hormone (0.05 mg/kg/day), oral glutamine (30 g/day), plus enteral nutrition for 4 weeks. Intestinal absorptive capacity and biochemical parameters were investigated before treatment and after treatment. Body composition was determined by bioelectric impedance analysis.* ***Result:*** *All patients completed the treatment. Intestinal absorptive capacity and plasma levels of proteins were significantly improved after treatment. Body weight, lean body mass, total body water, and body cell mass also increased without any major adverse effects. At the 3-month follow-up, the nutritional status of patients was also well maintained, and there was no death during this period.* ***Conclusion:*** *Four weeks of intestinal rehabilitation therapy significantly improved intestinal absorption if appropriate patient with short bowel syndrome was selected.*

Key words: Short bowel syndrome, growth hormone, glutamine, enteral nutrition

Kısa bağırsak sendromu olan hastalarda büyüme hormonu, glutamin ve enteral beslenmenin intestinal adaptasyon üzerindeki etkisi

Giriş ve Amaç: *Kısa barsak sendromunun tedavisinde, büyüme hormonunun, glutaminin ve enteral beslenmenin barsak adaptasyonuna olan etkisi halen tartışmalıdır. Bu çalışmanın amacı büyüme hormonu, glutamin ve enteral beslenmenin barsak adaptasyonuna katkısının araştırılmasıdır.* ***Gereç ve Yöntem:*** *Kısa barsak sendromu olan 12 hastaya (kalan ince barsak uzunluğu 59±9 cm) büyüme hormonu (0,05 mg/kg/gün), oral glutamin (30 mg/gün) ve enteral beslenme (4 hafta süre ile) uygulandı. Barsak absorbtif kapasitesi ve biyokimyasal parametreler tedaviden önce ve sonra incelendi. Vücut kompozisyonu biyoelektirik impedans yöntemi kullanılarak incelendi.* ***Bulgular:*** *Tüm hastalar tedaviyi tamamladı. Tedavi ertesinde barsak absorbtif kapasitesinde, plazma protein düzeylerinde belirgin düzelme kaydedildi. Hastaların kilo, kuru vücut ağırlığı, toplam vücut suyu ve hücre kütlesinde de artış kaydedildi ve ciddi yan etki tespit edilmedi. Üç aylık takipten sonra, ölüm görülmedi ve hastaların beslenme durumu iyiydi.* ***Sonuç:*** *İyi seçilmiş kısa barsak sendromlu hastalarda 4 haftalık rehabilitasyon uygulaması absorbtif kapasitede belirgin düzelme sağlamaktadır.*

Anahtar kelimeler: Kısa bağırsak sendromu, büyüme hormonu, glutamin, enteral beslenme

INTRODUCTION

Short bowel syndrome (SBS) is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet and results in chronic diarrhea, dehydration, fluid and electrolyte imbalances, and malnutrition (1).

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To maintain acceptable fluid, electrolyte, and nutritional balances, patients with SBS often require long-term parenteral nutrition (PN), which is expensive and associated with liver failure, repeated catheter sepsis, or venous thrombosis with loss of vascular access, resulting in failure of parenteral therapy (2-5). In patients who can no longer receive parenteral support, small bowel transplantation has been performed. The results of transplantation have improved but still remain disappointing. The long-term survival rate of intestinal transplantation is not high enough to be accepted as a routine procedure for some patients. Since the program of intestinal rehabilitation had been proposed in 1995 (6), it is hoped that some patients with SBS could be weaned from PN through intestinal compensation. However, the results of clinical studies are controversial (7-9).

The aim of the current study was to determine the effect of 4 weeks of treatment with recombinant human growth hormone (rhGH), glutamine (Gln), and enteral nutrition (EN) on intestinal adaptation in patients with SBS.

MATERIALS and METHODS

Patients

Twelve patients (9 men, 3 women; mean age 33±4 years, range 8-61years) with SBS were eligible for this study. Six had ileocecal valves and intact colon. All patients had previously undergone extensive bowel resection for small-bowel volvulus (n=4), intestinal obstruction (n=1), mesenteric infarction (n=4), Crohn's disease (n=1), and trauma (n=2). The average length of jejunum-ileum, as derived from operative reports and confirmed by radiographic examinations, was 59±9cm (range, 10-100 cm) in all patients. All patients received bowel rehabilitation therapy <2 years after massive intestinal resection, except one who received the therapy after 2.5 years.

Criteria for eligibility in the study were as follows: adults aged 18-70 years; the length of residual small bowel not exceeding 100 cm; acceptable liver and kidney function on admission; normal or stable cardiovascular status. Patients in an unstable condition such as sepsis, acute gastroenteritis, pneumonia, or previous exposure to GH were excluded.

All patients gave informed consent after receiving written information on the protocol. The protocol for the present study was approved by the Ethics Committee of Jinling Hospital.

Study Protocol

On admission, the first week served as control period. Since most patients with SBS had malnutrition and/or dehydration, to attain positive nitrogen balance and maintain adequate fluid and electrolyte balance, PN was started early in the majority of them. The total calories given according to the energy expenditure was determined by indirect calorimetry. Once this had been achieved, EN was started. To avoid EN-related gastrointestinal complications, EN enriched with dietary fiber (Nutrison Fibreboard, Nutricia Pharmaceutical (Wuxi, China) Co., Ltd.; 15 g dietary fiber in 1000 mL, 1.0 kcal/mL) was delivered gradually to the patients from 500 kcal/day to 1500-2000 kcal/day via nasogastric tube, or percutaneous endoscopic gastrostomy tube, or gastrostomy tube. The speed of transfusion was controlled at 25 mL/h with a peristaltic pump until the patients tolerated it well, and the speed was also increased. When EN exceeded 50% of patient's caloric requirement, PN was withdrawn gradually.

Intestinal rehabilitation therapy was initialed at the second in-hospital week. RhGH (Serono Inc, Switzerland) was administered subcutaneously at a dose of 0.05 mg/kg/day for 28 days. Supplemental Gln (Ajinomoto, Kawasaki City, Japan) was provided at 30 g/day by the oral route and was divided into three doses dissolved in warmed water.

Anti-diarrhea agents were given in patients with severe diarrhea when EN was initiated; commonly used drugs were diphenoxylate-atropine (Lomotil, Pfizer Inc., USA) or loperamide (Imodium, Johnson&Johnson Inc., USA). In addition, other drugs, such as vitamin D3, calcium, and anti-acids agents (omeprazole 40 mg/d in two divided dosage), were delivered if necessary.

On completion of the 28-day protocol, GH was discontinued, and the patients were discharged home on glutamine (30 g/day) and EN. When total EN was tolerated well, a high-carbohydrate, low-fat (HCLF) diet was added. The proportion of EN to HCLF diet depended on the capacity of absorption and patient's nutritional status.

Immediately before the treatment (baseline) and at the end of the treatment, a nutritional status (body weight, body composition) and intestinal absorptive function assessment were performed. In addition, a series of blood tests including the levels of plasma protein, albumin, and hemoglobin was assessed once a week. Follow-up data were collec-

ted at regular intervals and compared with the baseline data. The evaluation included patient's surviving times, body weight, defecate frequency, and serum proteins.

METHOD

Body Weight and Composition

Body weight was recorded in the morning, in light clothing after urinating and defecating, before breakfast, using a platform scale. Lean body mass, body fat, total body water, and body cell mass were measured by using bioelectric impedance analysis.

Intestinal Absorptive Function

The 72-hour nitrogen balance study was completed with each patient who could depend on EN to maintain daily resting energy expenditure. The progress of the study was as follows: the period began at 8 o'clock on the first day when patients were requested to urinate and defecate. During the 72-hour balance periods, all ad libitum oral intake and stool outputs were weighed, and the content of nitrogen was analyzed by using the Kjeldahl's method (10). The percentage absorption of nitrogen was calculated as [(oral intake-intestinal output)/oral intake]×100.

Statistics

Paired student's t-test was used for statistical analysis using the SPSS 16.0 (SPSS, Inc) software. A p-value of <0.05 was considered statistically significant. All data are expressed as means± SEM.

RESULTS

The baseline characteristics for each patient are shown in Table 1. All patients completed bowel rehabilitation therapy. Values on body weight and body composition are summarized in Table 2. After treatment with GH, Gln and EN, body weight increased by 3.04±0.92 kg ($p<0.05$), lean body mass increased by 2.39±0.63 kg ($p<0.05$), total body water increased by 1.76±0.49 ($p<0.05$), body cell mass increased by 1.66±0.45 ($p<0.05$), while body fat did not change significantly ($p>0.05$). Moreover, intestinal absorptive capacity was also significantly improved after treatment (Table 3).

Of the 12 patients, 11 were dependent on PN. Among the 11 patients, 5 were weaned off PN and lived on a modified diet supplement with EN from 500 to 1000 kcal/day (the minimal intestinal length of these patients was 25 cm with ileocecal valve and intact colon). One patient was weaned completely off PN and EN and lived on a modified diet. Four patients experienced a reduction in the volume and/or the frequency of PN that they required; the minimal intestinal length of these patients was 10 cm with a portion of colon in continuity without an ileocecal valve.

Table 1. Characteristics of the patients with SBS enrolled in the study

Patient ID	Sex/age (year)	Jejunal-ileal length (cm)	Ileocecal valve intact	Colon-in count (%)*	Diagnosis	Frequency of therapy	Delay since last surgery (year)	PN dependence (%)†
1	M/44	100	N	84	AWD	1	2.5	67
2	M/18	25	Y	100	SBV	1	1.5	67
3	M/38	100	N	84	IO	2	1	67
4	M/61	80	Y	100	MI	1	<1	67
5	M/32	50	Y	100	AWD	2	<1	75
6	M/33	80	Y	100	CD	1	<1	67
7	M/47	40	N	84	MI	2	<1	83
8	F/39	70	Y	100	MI	1	<1	67
9	M/31	35	N	100	SBV	2	<1	83
10	M/38	40	N	84	MI	1	<0.5	83
11	F/8	80	N	84	SBV	2	<0.5	67
12	F/8	10	Y	100	SBV	3	<0.5	91

CD: Crohn's disease. MI: Mesenteric infarction. SBV: Small-bowel volvulus. IO: Intestinal obstruction. AWD: Abdominal wall defect.
*According to Cummings et al (11). †In percent of total energy expenditure [(total PN energy deliver/resting energy expenditure)×100%].

Table 2. Body weight and body composition before and immediately after the treatment (n=12)

	Pre-treatment	Post-treatment	p-value
Body weight (kg)	49.53±3.99	52.57±3.91	0.007
Lean body mass (kg)	41.74±3.13	44.13±3.38	0.003
Body fat (kg)	7.78±1.29	8.80±1.17	0.244
Total body water (kg)	29.87±2.05	31.63±2.21	0.004
Body cell mass (kg)	28.20±2.41	29.86±2.50	0.004

Note. Results are expressed as mean±SEM.

Table 3. Intestinal absorptive capacity before and immediately after the treatment (n=12)

	Pre-treatment	Post-treatment	p-value
Absorptive rate of nitrogen (%)	59.16±2.93	79.13±1.07	0.000

Note. Results are expressed as mean±SEM.

Table 4. Body weight, defecation frequency, and selected blood values over the study period (n=12)

	Pre-treatment	Post-treatment	Follow-up
Body weight (kg)	49.53±3.99	52.57±3.91*	52.18±3.73*
defecate frequency (per day)	5.42±0.53	2.33±0.22*	2.83±0.32*
Total protein (g/L)	59.78±1.30	65.81±1.18*	64.83±1.66*
Albumin (g/L)	37.68±1.28	41.25±1.32*	41.48±1.33*
Hemoglobin (g/L)	110.58±5.67	118.42±3.77	114.42±4.18

Note. Results are expressed as mean±SEM. *p<0.01; post-treatment and follow-up vs. pre-treatment values.

Minor adverse effects occurred in some patients, but not all patients, during the study. Two patients complained of diarrhea after tube feeding, which resulted from cold temperature and was controlled by warming the EN along the feeding tube. Three patients noticed slight stiffness of joints at the beginning of treatment with GH. This discomfort seemed to be minor and did not justify any particular treatment. With discontinuation of GH, all symptoms related to the drug resolved in all subjects.

The length of follow-up was between 3 months and 1 year, and no deaths occurred among the patients during this period. Frequency of stool increased slightly but remained reduced compared to pre-treatment values ($p<0.05$). Nutritional status was well maintained, body weight deceased but still remained within ideal body weight range (Table 4).

DISCUSSION

In this open-label trial, we studied the effect of GH, Gln, and EN on intestinal adaptation in patients with SBS. Patients receiving this therapy decreased or were even completely weaned off PN requirements by 4-week treatment compared with baseline. During the treatment, patients maintained an appropriate body weight and nutritional status while PN was reduced or weaned off suggestion that compensatory events in the residual intestine had occurred. Thus, this therapy appears useful to aid intestinal adaptation in patients with SBS.

The intestine has an inherent ability to adapt in response to internal and external environmental stimuli (12,13). Following intestinal resection, residual intestine undergoes adaptation and nutritional autonomy may be obtained. However, intestinal adaptation is a fairly long and complex process and is influenced by several factors.

The length of the residual intestine is the key factor which significantly influences the intestinal adaptation. The longer the residual intestine, the greater the tendency to wean from PN. In the current study, almost all patients with intestinal length >60 cm had favorable outcomes compared

with those with shorter intestinal length. In addition, the quality of the residual intestine is another important factor influencing the adaptive potential of the residual intestine. As suggested by Byrne et al (14), the presence of active disease (e.g. Crohn's disease) in the residual intestine has an inhibitory effect on intestinal compensation, and rehabilitation efforts should be delayed in patients with active disease until the primary disease process is in remission.

The presence of ileocecal valve and the colon, which reduce the gastrointestinal transit time and increase the absorption of water and electrolyte, is another important factor determining the adaptation of patients with SBS. The presence of an ileocecal valve may allow independence from PN in patients with short bowel lengths. In the current study, the patients with an ileocecal valve and intact colon had a more optimistic outcome than patients without ileocecal valve.

Age is also an important factor affecting patient outcome. It has been reported that the capacity of intestinal compensation in paediatric short bowel syndrome patients is superior to the adults (15). In the current study, one paediatric patient (patient 11) had been weaned off PN completely and lived on a modified diet supplement with EN 500 kcal/day, while another aged patient (patient 4) just reduced the requirements of PN.

The interval between intestinal resection and the initial treatment is a determinate factor in the efficacy of bowel rehabilitation therapy. Intestinal adaptation often occurs within 2 months to 2 years after massive intestine resection (16). In a study of Byrne et al (6), the average time from intestinal resection to rehabilitation therapy was 6±1 years; 40% patients were weaned off PN, and an additional 40% have reduced their PN requirements. On the contrary, Scolapio's patients had been dependent on PN for an average of 12.9 years, thus, the absorption of macronutrient or fluid did not increase, and no patients were weaned off PN (17). In our research, one patient received bowel rehabilitation therapy 2.5 years after intestinal resection. His intestinal compensation was not significant, and the defecate frequency reduced temporarily compared with patients receiving bowel rehabilitation therapy within 2 years after intestinal resection.

Over the past decade, though both open-label and blinded studies have been performed, the results are controversial. Some studies (8, 17) failed to observe significant intestinal compensation, while others (6, 18) noted improvement of intestinal absorption. From the current trial and previous studies, we know that the efficacy of therapy in the adaptive response of the small bowel may be based heavily upon the clinical status of the patient. So in order for the therapy to be successful, appropriate patient selection is imperative.

In conclusion, the results of our study suggest that treatment with GH, Gln, and EN is useful to aid intestinal adaptation if appropriate patient is selected.

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