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Original Article

Effect of early oral nutrition supplement using Encover in patients undergoing hepato-biliary-pancreatic surgery

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Backgrounds/Aims: Early recovery after surgery has become a popular trend. The aim of this study was to evaluate effect of nutritional intervention using Encover, an oral nutritional supplement, in patients undergoing hepato-biliary-pancreatic surgery.
Methods: This single center, prospective case-control study was conducted in Gangnam Severance Hospital from September 2018 to April 2019. Through randomization, patients were divided into an experimental group (30 patients) and a control group (30 patients). At postoperative seven days, the experimental group was instructed to take two packs of Encover (JW Pharmaceutical, Seoul, Korea) daily for seven days. Body cell mass index was measured at seven days after surgery and 14 days after discharge and Patient-Generated Subjective Global Assessment (PG-SGA) was performed at 14 days after discharge.
Results: Body cell mass index during outpatient follow-up was significantly decreased compared to that at discharge in both groups. However, the amount of body cell mass index showed no significant difference between postoperative seven days and outpatient follow-up in either group. During outpatient follow-up, the experimental group had a higher mean value of PG-SGA score than the control group (11.32 ± 3.46 vs. 9.48 ± 3.97; $p = 0.037$).
Conclusions: Short-term Encover doses after surgery may not produce significant results in weight gain or other body cell mass index. Encover did not significantly affect other dietary conditions based on PG-SGA.

Key Words: Nutritional support; Supplementary feeding; Diertary supplements; Enhanced recovery after surgery; Enteral nutrition

INTRODUCTION

It has been reported that 20% to 50% of hospitalized patients are malnourished, with nutritional status worsening during hospitalization [1-4]. Poor dietary intake during hospitalization can cause deterioration of nutritional status. Malnutrition can increase complications including infection. It can also increase hospital stay and mortality [3,5,6]. Thus, appropriate nutritional therapy is needed. It is essential to point out areas to raise awareness for medical staff. In particular, in the case of gastrointestinal cancer, catabolism increases up to 10 days after surgery while protein anabolic activity decreases, which can result in loss of intestinal and skeletal muscle proteins in the body, postoperative weight loss, and cachexia, leading to decreased ability to recover for the body [4,7].

Recent surgical trends are focusing on early recovery after surgery. Enhanced Recovery After Surgery has been introduced. Early nutrition is strongly recommended for rapid recovery and proper nutrition of surgical patients [8-10]. However, when having a liquid to soft food diet after surgery, it is difficult to meet nutritional requirements due to the low caloric content per unit volume. After surgery, nutritional adequacy of a patient should be carefully reviewed due to problems such as indigestion, early postprandial fullness, bloating, and restriction of one-time meal intake [11,12]. Therefore, it is important to provide patients with a diet having proper amounts and adequate calories for sufficient nutrition to help their recovery.

Encover (JW Pharmaceutical, Seoul, Korea) is a product developed for patients who have difficulty in eating or lack nutritional intake [13,14]. It is an enteral nutrient that is used for tuberous nutrition, especially when oral nutrition is difficult for a long period of time. Patients who undergo major hepato-bil-

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iary-pancreatic surgery have a relatively low survival rate. Low body weight (body mass index [BMI] < 18.5 kg/m^2) is directly related to the factors that increase the 5-year survival rate, which is less than 20% [15]. Intake of Encover is expected to improve body weight and biochemical/human measurements by contributing to continuous nutritional supplementation and increasing energy and protein intake. It is thought that it can increase survival rate by improving the quality of life of patients with liver and gallbladder disease.

The purpose of this study was to evaluate the effect of nutritional supplementation using Encover, an oral nutritional supplement, in patients undergoing major hepato-biliary-pancreatic surgery. Changes in weight, body fat, and muscle mass were determined after additional Encover was taken after surgery.

MATERIALS AND METHODS

Study design and period

This was a single center, randomized case control study. It was conducted from September 2018 to April 2019. Patients in the Hepatobiliopancreatic Cancer Clinic, Gangnam Severance Hospital, Yonsei University College of Medicine were recruited. This study was approved by Gangnam Severance Institutional Review Board (approval number: 3-2017-0222). Written informed consent was obtained from all participants.

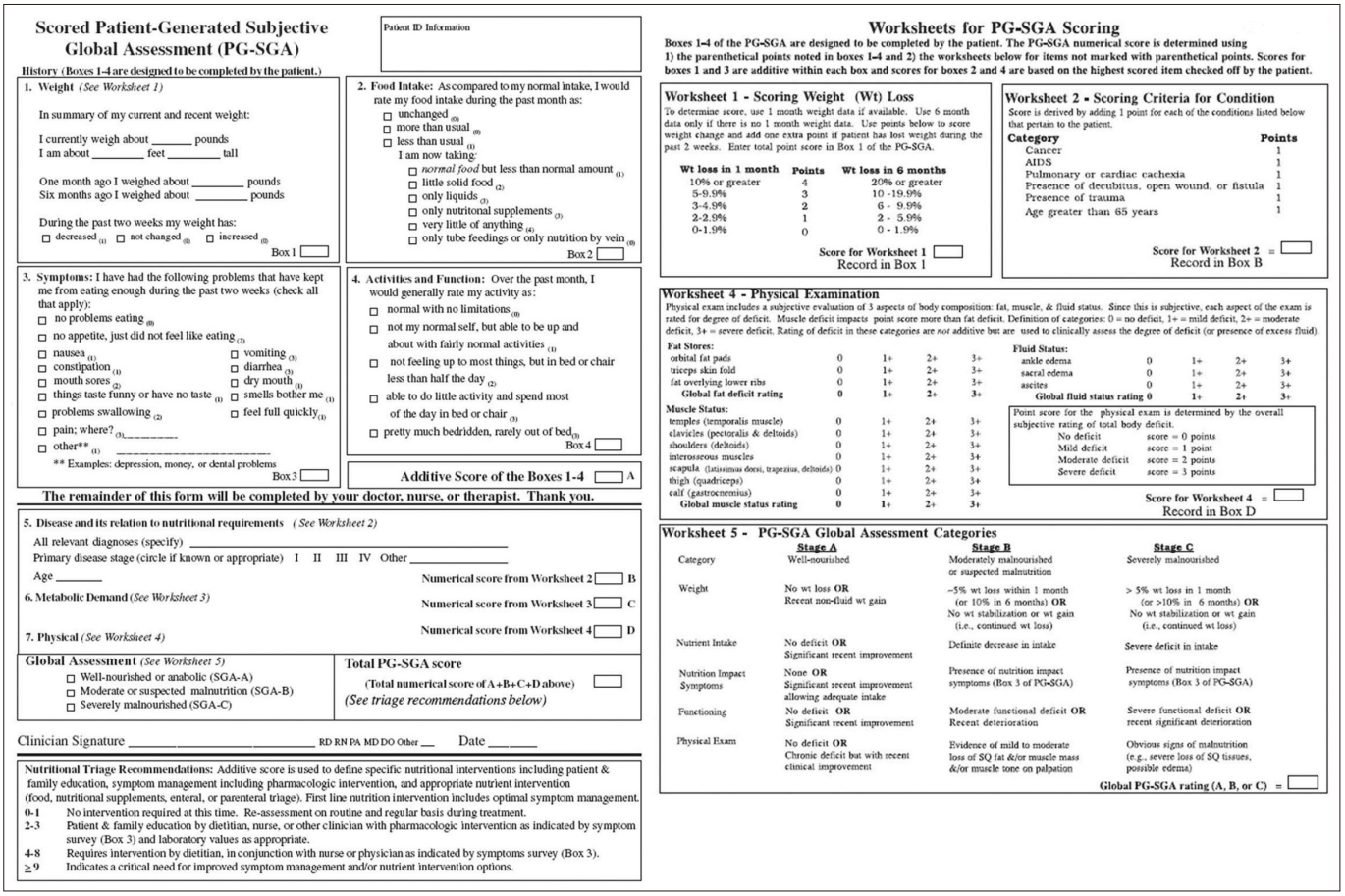
Patient selection and enrollment criteria

Inclusion criteria

- Patients scheduled for major hepato-biliary-pancreatic surgery
- Major hepato-biliary-pancreatic surgery: segmentectomy, hemihepatectomy, segmental resection of bile duct, radical cholecystectomy, distal pancratectomy, pancreatodudenectomy

Exclusion criteria

- Patient with poor adherence to oral nutritional supplements
- Liver failure or renal failure patients
- Patient unable to intake food orally
- Patient with severe ascites and edema affecting weight evaluation
- Patient whose cancer has metastasized to the brain


Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Patient ID Information

History (Boxes 1-4 are designed to be completed by the patient.)

1. Weight (See Worksheet 1)
In summary of my current and recent weight:
I currently weigh about _____ pounds
I am about _____ feet _____ tall
One month ago I weighed about _____ pounds
Six months ago I weighed about _____ pounds
During the past two weeks my weight has:
☐ decreased (1) ☐ not changed (0) ☐ increased (0)
Box 1 ☐

2. Food Intake: As compared to my normal intake, I would rate my food intake during the past month as:
☐ unchanged (0)
☐ more than usual (0)
☐ less than usual (1)
I am now taking:
☐ normal food but less than normal amount (1)
☐ little solid food (2)
☐ only liquids (3)
☐ only nutritonal supplements (3)
☐ very little of anything (4)
☐ only tube feedings or only nutrition by vein (0)
Box 2 ☐

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply):
☐ no problems eating (0)
☐ no appetite, just did not feel like eating (3)
☐ nausea (1) ☐ vomiting (3)
☐ constipation (1) ☐ diarrhea (3)
☐ mouth sores (2) ☐ dry mouth (0)
☐ things taste funny or have no taste (1) ☐ smells bother me (1)
☐ problems swallowing (2) ☐ feel full quickly (1)
☐ pain; where? (3)_____
☐ other** (1) _____
** Examples: depression, money, or dental problems
Box 3 ☐

4. Activities and Function: Over the past month, I would generally rate my activity as:
☐ normal with no limitations (0)
☐ not my normal self, but able to be up and about with fairly normal activities (1)
☐ not feeling up to most things, but in bed or chair less than half the day (2)
☐ able to do little activity and spend most of the day in bed or chair (3)
☐ pretty much bedridden, rarely out of bed (3)
Box 4 ☐

Additive Score of the Boxes 1-4 ☐ A

The remainder of this form will be completed by your doctor, nurse, or therapist. Thank you.

5. Disease and its relation to nutritional requirements (See Worksheet 2)
All relevant diagnoses (specify) _____
Primary disease stage (circle if known or appropriate) I II III IV Other _____
Age _____
Numerical score from Worksheet 2 ☐ B

6. Metabolic Demand (See Worksheet 3)
Numerical score from Worksheet 3 ☐ C

7. Physical (See Worksheet 4)
Numerical score from Worksheet 4 ☐ D

Global Assessment (See Worksheet 5)
☐ Well-nourished or anabolic (SGA-A)
☐ Moderate or suspected malnutrition (SGA-B)
☐ Severely malnourished (SGA-C)

Total PG-SGA score
(Total numerical score of A+B+C+D above) ☐
(See triage recommendations below)

Clinician Signature _____ RD RN PA MD DO Other __ Date _____

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage). First line nutrition intervention includes optimal symptom management.

0-1	No intervention required at this time. Re-assessment on routine and regular basis during treatment.
2-3	Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and laboratory values as appropriate.
4-8	Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms survey (Box 3).
≥9	Indicates a critical need for improved symptom management and/or nutrient intervention options.

Worksheets for PG-SGA Scoring

Boxes 1-4 of the PG-SGA are designed to be completed by the patient. The PG-SGA numerical score is determined using 1) the parenthetical points noted in boxes 1-4 and 2) the worksheets below for items not marked with parenthetical points. Scores for boxes 1 and 3 are additive within each box and scores for boxes 2 and 4 are based on the highest scored item checked off by the patient.

Worksheet 1 - Scoring Weight (Wt) Loss

To determine score, use 1 month weight data if available. Use 6 month data only if there is no 1 month weight data. Use points below to score weight change and add one extra point if patient has lost weight during the past 2 weeks. Enter total point score in Box 1 of the PG-SGA.

Wt loss in 1 month	Points	Wt loss in 6 months
10% or greater	4	20% or greater
5-9.9%	3	10 -19.9%
3-4.9%	2	6 - 9.9%
2-2.9%	1	2 - 5.9%
0-1.9%	0	0 - 1.9%

Score for Worksheet 1 ☐
Record in Box 1

Worksheet 2 - Scoring Criteria for Condition

Score is derived by adding 1 point for each of the conditions listed below that pertain to the patient.

Category	Points
Cancer	1
AIDS	1
Pulmonary or cardiac cachexia	1
Presence of decubitus, open wound, or fistula	1
Presence of trauma	1
Age greater than 65 years	1

Score for Worksheet 2 = ☐
Record in Box B

Worksheet 4 - Physical Examination

Physical exam includes a subjective evaluation of 3 aspects of body composition: fat, muscle, & fluid status. Since this is subjective, each aspect of the exam is rated for degree of deficit. Muscle deficit impacts point score more than fat deficit. Definition of categories: 0 = no deficit, 1+ = mild deficit, 2+ = moderate deficit, 3+ = severe deficit. Rating of deficit in these categories are *not* additive but are used to clinically assess the degree of deficit (or presence of excess fluid).

Fat Stores:				
orbital fat pads	0	1+	2+	3+
triceps skin fold	0	1+	2+	3+
fat overlying lower ribs	0	1+	2+	3+
Global fat deficit rating	0	1+	2+	3+
Muscle Status:				
temples (temporalis muscle)	0	1+	2+	3+
clavicles (pectoralis & deltoids)	0	1+	2+	3+
shoulders (deltoids)	0	1+	2+	3+
interosseous muscles	0	1+	2+	3+
scapula (latissimus dorsi, trapezius, deltoids)	0	1+	2+	3+
thigh (quadriceps)	0	1+	2+	3+
calf (gastrocnemius)	0	1+	2+	3+
Global muscle status rating	0	1+	2+	3+

Fluid Status:				
ankle edema	0	1+	2+	3+
sacral edema	0	1+	2+	3+
ascites	0	1+	2+	3+
Global fluid status rating	0	1+	2+	3+

Point score for the physical exam is determined by the overall subjective rating of total body deficit.

No deficit	score = 0 points
Mild deficit	score = 1 point
Moderate deficit	score = 2 points
Severe deficit	score = 3 points

Score for Worksheet 4 = ☐
Record in Box D

Worksheet 5 - PG-SGA Global Assessment Categories

	Stage A	Stage B	Stage C
Category	Well-nourished	Moderately malnourished or suspected malnutrition	Severely malnourished
Weight	No wt loss OR Recent non-fluid wt gain	~5% wt loss within 1 month (or 10% in 6 months) OR No wt stabilization or wt gain (i.e., continued wt loss)	> 5% wt loss in 1 month (or >10% in 6 months) OR No wt stabilization or wt gain (i.e., continued wt loss)
Nutrient Intake	No deficit OR Significant recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms	None OR Significant recent improvement allowing adequate intake	Presence of nutrition impact symptoms (Box 3 of PG-SGA)	Presence of nutrition impact symptoms (Box 3 of PG-SGA)
Functioning	No deficit OR Significant recent improvement	Moderate functional deficit OR Recent deterioration	Severe functional deficit OR recent significant deterioration
Physical Exam	No deficit OR Chronic deficit but with recent clinical improvement	Evidence of mild to moderate loss of SQ fat &/or muscle mass &/or muscle tone on palpation	Obvious signs of malnutrition (e.g., severe loss of SQ tissues, possible edema)

Global PG-SGA rating (A, B, or C) = ☐

Fig. 1. Patient-Generated Subjective Global Assessment sheet.

- Patient who have difficulty controlling blood sugar
- Patient with BMI > 30 kg/m^2
- Illiteracy/foreign patient
- Patient with contraindications for Encover administration

Sample size calculation

The output of the sample size was based on an independent two-sample t-test. The expected ratio of maintaining muscle mass was determined by referring to a paper previously published by Kim et al. [16] Assuming an alpha value of 0.05 and 1-β (power) of 0.8, 22.271 samples would be needed for each group. Considering a dropout rate of 30%, 30 samples would be needed for each group.

Perioperative evaluation and intervention

All patients who were potential candidates for major hepato-biliary-pancreatic surgery were informed about this study. Only patients who voluntarily consented participated in this study. Patients who agreed to participate in this study were assigned to either a control group or an experimental group by randomization. Randomization was take place via an allocation randomization system before surgery. Patients were randomized to one of the two groups at a 1 : 1 ratio.

After patients were enrolled, their baseline characteristics were recorded. Patient-Generated Subjective Global Assessment (PG-SGA) (Fig. 1) was used to evaluate and record their current nutritional status. Body cell mass index measurements (Inbody S-10; Biospace, Seoul, Korea) were taken before surgery. At postoperative seven days, body cell mass index measurement was taken again. Patients were excluded from this study if they could not tolerate soft diet and/or refused to take Encover on postoperative seven days. At this time, the experimental group was instructed to take two packs of Encover daily for seven days while the control group was not instructed to take it. At 14 days after discharge, the last body cell mass index measurement was taken. PG-SGA was performed during outpatient follow-up. Patients taking less than 7 packs in total were excluded from this study. During the study period, a total of 8 cases were excluded from the Encover group as study denied or under dose in the experimental group. A total of 3 cases withdrew from this study due to operation hold, study denied, or complications in the control group (Fig. 2).

Statistical analysis

All statistical analyses were performed using IBM SPSS software, ver. 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were analyzed either by chi-squared test or Fisher's exact test, while continuous variables were analyzed using Student's t-test or Mann–Whitney U test. Statistical significance was considered when p-value was less than 0.05.

RESULTS

Clinicopathologic characteristics of patients are presented in Table 1. There was no significant difference in sex, age, or perioperative laboratory data related to nutritional status (such as albumin, prealbumin, cholesterol) between the control group and the experimental group. Major diagnosis, open and laparoscopic ratio, and main operation site (liver or pancreas) did not differ between the two groups either. Preoperative body cell mass index did not show significant difference between the two groups either (Table 2). During outpatient follow-up, body weight, body cell mass, soft lean mass, and fat free mass, but not fat mass, were significantly decreased than those at postoperative seven days in both groups (Table 3). When comparing the amount of change in body cell mass index from postoperative seven days to outpatient follow-up, there was no difference between the two groups. Body weight was decreased by 3.82 ± 2.84 kg in the control group and 4.27 ± 3.65 kg in the experimental group, showing no significant difference between the two (p = 0.627). There was no significant difference in the amount of change in body cell mass (p = 0.684), soft lean mass

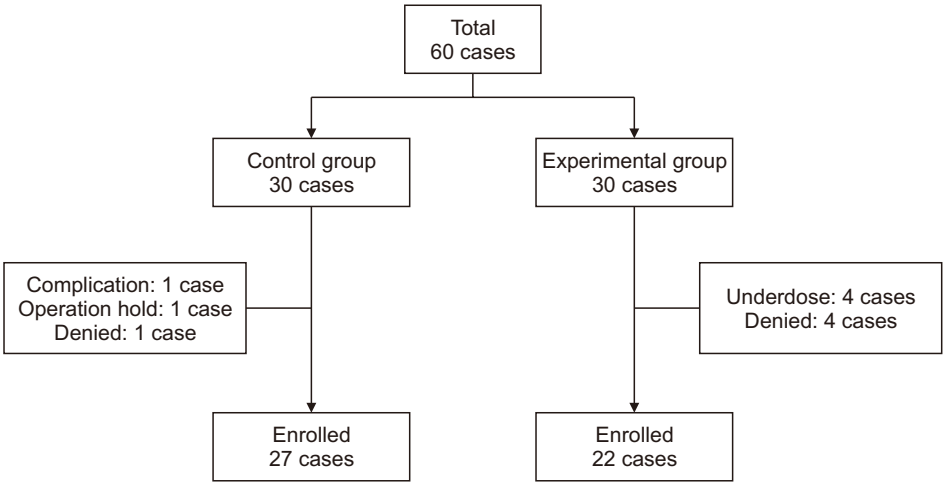


Fig. 2. Case enrollment diagram.

Table 1. Clinicopathologic characteristics of subjects

Variable	Control group (27 cases)	Experimental group (22 cases)	*p*-value
Sex (male : female)	15 (55.6) : 12 (44.4)	16 (72.7) : 6 (27.3)	0.248
Age (yr)	61.5 ± 13.43	67.0 ± 10.09	0.120
Major diagnosis			0.813
HCC	14 (51.9)	11 (50.0)	
CCLM	4 (14.8)	6 (27.3)	
CCC	3 (11.1)	2 (9.1)	
Pancreatic cancer	3 (11.1)	2 (9.1)	
Benign liver disease	2 (7.4)	0 (0)	
Benign pancreas disease	1 (3.7)	1 (4.5)	
Operation (Open : Lapa)	11 (40.7) : 16 (59.3)	10 (45.5) : 12 (54.5)	0.740
Operation (liver : pancreas)	23 (85.2) : 4 (14.8)	19 (86.4) : 3 (13.6)	1.000
Laboratory data			
Preop. albumin (g/dL)	4.0 ± 0.4	4.1 ± 0.4	0.376
Postop. albumin (g/dL)	3.2 ± 0.5	3.1 ± 0.3	0.772
Preop. cholesterol (mg/dL)	162.7 ± 41.9	155.3 ± 41.1	0.538
Postop. cholesterol (mg/dL)	112.7 ± 25.6	111.9 ± 30.4	0.922
Postop. pre-albumin (mg/L)	93.4 ± 26.1	90.6 ± 28.6	0.720

Values are presented as number (%) or mean ± standard deviation.
HCC, hepatocellular carcinoma; CCLM, colon cancer liver metastasis; CCC, cholangiocellular carcinoma; Open, conventional open operation; Lapa, laparoscopic operations; Preop., preoperative; Postop., postoperative.

(p = 0.561), fat free mass (p = 0.578), or fat mass (p = 0.834) between the two groups either (Table 4).

When PG-SGA score and grade were compared, there was no difference in preoperative PG-SGA score or grade between the two groups. However, during postoperative outpatient follow-up, the experimental group had higher mean PG-SGA score (p = 0.037) and PG-SGA grade (p = 0.032) than the control group (Table 5).

DISCUSSION

This study was conducted in patients who underwent hepato-biliary-pancreatic surgery. The purpose of this study was to determine the effect of nutritional supplement using Encover by comparing postoperative body cell mass index following administration of additional oral nutritional supplements.

In this study, body cell mass index analysis was performed using the multi-frequency impedance method with Inbody S-10. This method has been used in many studies as a simple and effective method to indirectly measure the body cell mass index [17-19]. PG-SGA is also widely used as a tool to evaluate the nutritional status of patients by examining changes in body weight, changes in meal intake, problems related to meals, and the level of physical activity through interviews with experi-

Table 2. Preoperative body cell mass index difference between the experimental group and the control group

Variable	Control group (27 cases)	Experimental group (22 cases)	*p*-value
Body weight (kg)	64.75 ± 12.13	66.03 ± 12.01	0.715
Body cell mass (kg)	32.02 ± 7.80	32.77 ± 5.37	0.693
Soft lean mass (kg)	46.30 ± 10.78	47.50 ± 7.66	0.660
Fat free mass (kg)	49.20 ± 11.37	50.40 ± 8.06	0.677
Fat mass (kg)	15.56 ± 7.69	15.62 ± 7.20	0.975

Values are presented as mean ± standard deviation.

Table 3. Body cell mass index at postoperative seven days and outpatient follow-up

Variable	Discharge	OPD F/U	*p*-value
Body weight (kg)			
Control group (27 cases)	65.8 ± 11.50	62.0 ± 11.36	< 0.001
Experimental group (22 cases)	66.6 ± 11.18	62.3 ± 9.67	< 0.001
Body cell mass (kg)			
Control group (27 cases)	32.2 ± 7.07	30.1 ± 6.67	< 0.001
Experimental group (22 cases)	32.7 ± 5.21	30.2 ± 5.04	< 0.001
Soft lean mass (kg)			
Control group (27 cases)	47.6 ± 9.72	44.1 ± 9.15	< 0.001
Experimental group (22 cases)	48.3 ± 7.69	44.2 ± 7.30	< 0.001
Fat free mass (kg)			
Control group (27 cases)	50.7 ± 10.22	47.0 ± 9.59	< 0.001
Experimental group (22 cases)	51.4 ± 8.11	47.0 ± 7.68	< 0.001
Fat mass (kg)			
Control group (27 cases)	15.1 ± 7.60	15.1 ± 7.14	0.900
Experimental group (22 cases)	15.2 ± 7.29	15.3 ± 6.40	0.870

Values are presented as mean ± standard deviation.
OPD F/U, outpatient follow-up.

Table 4. Change amount in body cell mass index between postoperative seven days and outpatient follow-up

Variable	Change amount	*p*-value
Body weight (kg)		0.627
Control group (27 cases)	–3.82 ± 2.84	
Experimental group (22 cases)	–4.27 ± 3.65	
Body cell mas (kg)		0.684
Control group (27 cases)	–2.19 ± 2.43	
Experimental group (22 cases)	–2.45 ± 1.92	
Soft lean mass (kg)		0.561
Control group (27 cases)	–3.46 ± 3.83	
Experimental group (22 cases)	–4.06 ± 3.16	
Fat free mass (kg)		0.578
Control group (27 cases)	3.75 ± 4.07	
Experimental group (22 cases)	–4.36 ± 3.36	
Fat mass (kg)		0.834
Control group (27 cases)	–0.07 ± 2.64	
Experimental group (22 cases)	0.09 ± 2.39	

Values are presented as mean ± standard deviation.

Table 5. PG-SGA score and grade

Variable	Control group (27 cases)	Experimental group (22 cases)	*p*-value
PG-SGA Score			
Preop.	5.48 ± 4.06	5.50 ± 2.81	0.590
OPD F/U	9.48 ± 3.97	11.32 ± 3.46	0.037
PG-SGA Grade			
Preop.	1.30 ± 0.67	1.27 ± 0.63	0.990
OPD F/U	2.00 ± 0.83	2.50 ± 0.60	0.032

Values are presented as mean ± standard deviation.
PG-SGA, Patient-Generated Subjective Global Assessment; Preop., preoperative; OPD F/U, outpatient follow-up.

enced nutritionists [20-22]. Nutritional risk screening 2002 method (NRS-2002) can also be used as a tool to evaluate nutritional status. However, PG-SGA is generally reported to have higher sensitivity than NRS-2002 [23,24].

Reduction of lean mass is associated with delayed wound healing, increased infection rate, increased morbidity, increased hospital stay, and increased medical costs for patients at risk of malnutrition such as surgical patients and critically ill patients [25]. It has been reported that reduction of lean mass has a strong correlation with increased mortality and organ failure [26]. In our study, most patients showed significant reductions in weight, body cell mass, lean mass, and muscle mass during outpatient follow-up compared to those before discharge.

The experimental group was given two packs of Encover per day for seven days. The total daily dose had 400 calories. The additional dose had 2,800 calories compared to the control group. Although each person's food intake and digestibility might vary, one gram of protein is equivalent to about four kilocalories. Thus, simply adding one kilogram of fat requires 4,000 kilocalories. Although our study aimed to suppress decrease in body cell mass index through additional nutritional supplement, calories of additional nutritional supplement were limited.

Just as kidney patients need dialysis treatment and respiratory patients need ventilator, oral nutrition is an essential treatment for digestive disorder patients [27]. Taking Encover during the early recovery period after surgery for a short period of time is ineffective for diet weight gain. Other body cell mass indices (body cell mass, body fat, lean mass, muscle mass) were not significant changed either. Thus, it can be concluded that short-term effects of oral nutritional supplements could not affect body cell mass index. In addition, PG-SGA score and grade at outpatient follow-up were higher than those in the control group, indicating malnutrition in the experimental group.

Previous study have hypothesized that insufficient oral food intake is correlated with satiety and volume in the digestive tract [16]. Therefore, oral nutritional supplements such as high energy density in the diet are expected to help increase final caloric intake and subjective nutritional indicators after ingestion. However, PG-SGA score and grade showed opposite results. Taking Encover two packs a day might have reduced their original normal meal intake due to worsening of gastrointestinal satiety. This is a short-term side effect, suggesting that additional oral nutritional supplements may affect dietary intake. Additional oral nutritional supplements cannot be free from risks such as reduced intake of regular meals that can be better absorbed. In the future, in terms of nutritional management, when taking alternative nutrients, it is necessary to continuously monitor patient's subjective nutritional status and closely monitor whether there is a possibility of digestive disorders or reduced intake.

This study has some limitations. First, it did not have a long-term follow-up after surgery. Interference aspects such as uncontrolled variables (gastrointestinal trouble) should also be considered. The effect on energy consumption rate according to the difference in exercise amount after each patient's operation cannot be completely excluded.

In future studies, rather than using a short one-week dose period, we intend to investigate difference in body cell mass index according to the increase or decrease in dose by considering expansion and consumption of Encover as continuous variables.

In conclusion, short-term Encover doses after surgery may not produce significant results in weight gain or other body cell mass index. In addition, Encover does not significantly affect other dietary conditions based on PG-SGA.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: DSY, JHL. Data curation: BJL. Methodology: JSP, DSY. Visualization: HSK. Writing - original draft: BJL. Writing - review & editing: JHL.

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