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Original Article

Randomized controlled trial on efficacy of oligomeric formula (HINE E-GEL®) versus polymeric formula (MEIN®) enteral nutrition after esophagectomy for esophageal cancer with gastric tube reconstruction

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SUMMARY. **The efficacy of early enteral nutrition after esophageal cancer surgery has been reported. However, the choice of formula and management of diarrhea are important to achieve the goal of enhanced recovery after surgery. The aim of this study is to assess the frequency of diarrhea/completion rate of enteral nutrition regimen as primary endpoints and the postoperative nutritional status/body composition analysis/operative morbidity as secondary endpoints was compared between the two nutrition groups. Among the 122 patients who underwent esophagectomy for esophageal cancer between December 2015 and September 2017, 67 patients who met the eligibility criteria were randomly assigned to receive enteral nutrition with either HINE E-GEL® (HINE group; $n = 33$) or MEIN® (MEIN group; $n = 34$). The incidence of diarrhea was significantly lower in the HINE group (18.2 % vs. 64.7 %, $P < 0.001$). The score of Bristol scale of POD 6/7 was significantly lower in the HINE group ($P = 0.019$/$P = 0.006$, respectively). The completion rate of enteral nutrition regimen was significantly higher in the HINE group (97.4 % vs. 86.6 %, $P = 0.002$). The Controlling Nutritional Status scores and total protein levels at 6 months after surgery were significantly better in the HINE group ($P = 0.030$ and $P = 0.023$, respectively), indicating improved tendency in nutritional status in the HINE group. However, there were no significant differences in Prognostic Nutritional Index values, blood test results, rapid turnover proteins, body mass index, or body composition between the two groups. HINE E-GEL compared with MEIN may reduce the frequency of diarrhea, enabling patients to adhere to the scheduled enteral nutrition plan. Also, maintenance of nutritional status with HINE E-GEL was comparable or potentially better in some nutrition components to that with MEIN, indicating that HINE E-GEL can be an option for enteral nutrition following esophageal surgery to achieve the goal of successful completion of scheduled enteral nutrition and smooth transition to the normal diet.**

KEY WORDS: **enteral nutrition, esophageal cancer gastric tube reconstruction, HINE E-GEL, MEIN.**

INTRODUCTION

Early postoperative enteral nutrition is beneficial in facilitating wound healing and alleviating postoperative complications[1–5] as well as suppressing excessive inflammatory response and exerting immunologically beneficial effect after esophageal cancer surgery, which is one of the most invasive gastroenterological surgeries.[6–8] We currently use a polymeric formula MEIN® for enteral nutrition after esophageal cancer surgery. MEIN, fortified with whey peptides and the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is a form of immunonutrition that exerts postoperative anti-inflammatory, antioxidant, antibacterial, and immune-modulating effects.[7,8] Clinical benefits, such as reduced incidence of postoperative complications and shortened duration of hospitalization, have also been shown.[9] In the actual clinical settings, however, some patients require change of formula because of severe diarrhea accompanied by administrating the conventional enteral nutritional formula. Therefore, choice of enteral formula may be important to reduce

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the diarrhea and to achieve the goal of successful completion of scheduled enteral nutrition and smooth transition to the normal diet. HINE E-GEL® is a milk protein-free and low osmotic load oligomeric formula with a carbohydrate–fat–protein energy ratio comparable with that of MEIN. This randomized controlled study compares the frequency of diarrhea as a postoperative complication and the intermediate- and long-term nutritional status between the two formulas to identify the optimum postoperative enteral nutrition formula.

PATIENTS AND METHODS

Study design and endpoints

This study protocol was conducted with approval from the Institutional Review Board of Toranomon Hospital (the approval No: IRB number 1133) and was registered at the UMIN Clinical Trials Registry (UMIN-CTR, R000024297). The procedures were conducted in accordance with the ethical standards of the Helsinki Declaration of 1975. Informed consent was obtained from all participants preoperatively. A prospective randomized controlled trial was designed to compare the efficacy of the oligomeric formula (HINE E-GEL; Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan) and the polymeric formula (MEIN®; Meiji Dairies Co., Tokyo, Japan) after esophagectomy for esophageal cancer with gastric tube reconstruction. Continuous enteral nutrition was started on postoperative day 2 at 10 mL/hour. The feeding rate was increased every day by 10 mL/hour, with careful observation of physical conditions and X-ray findings, to 60 mL/hour on postoperative day 7. The oral feeding was started on postoperative day 8. We gradually adjusted the amount of enteral nutrition intake according to the amount of oral food intake for each patient. Many patients are able to stop the enteral nutrition intake at the time of discharge. On the other hand, in case of anastomotic leakage or other problems related to oral feeding resumption, the enteral nutrition was continued. When the daily frequency of passing diarrheal stool exceeded 6, the feeding rate was reverted to the level of the previous day. When a daily frequency of passing diarrheal stool $\geq$6 was observed even at a reduced feeding rate, a different formula expected to cause less diarrhea replaced the existing enteral nutrition formula at the same feeding rate. Enteral nutrition was stopped immediately if allergic reactions occurred.

Primary endpoints were frequency of diarrhea, fecal condition using the Bristol Stool Form Scale[10] and completion rate of enteral nutrition regimen. Secondary endpoints were operative morbidity, nutritional status (rapid turnover proteins, weight change), laboratory data, length of stay in intensive care unit (ICU), postoperative hospital stay, body composition analysis (skeletal muscle mass, body fat percentage, etc.). We diagnosed diarrhea as types 6 and 7 on the Bristol Stool Form Scale.[10] The completion rate of the enteral nutrition regimen was calculated with the following expression: = {(Days of enteral nutrition without reduction, discontinuation, or change in the formula)/7 days} × 100 (%). Disease was staged according to the Union for International Cancer Control (UICC) TNM grading system, 7th edition.[11] We graded all postoperative complications based on the Clavien–Dindo classification,[12] and grade $\geq$2 events were documented as complications.

Study population and eligibility criteria (Figure 1)

Between December 2015 and September 2017, 122 consecutive patients with esophageal cancer who underwent esophagectomy were assessed for trial eligibility. Patients were randomized into two groups after surgery using a random numbers table, HINE group to receive 6 days of postoperative supplementation of the oligomeric formula (HINE E-GEL) and MEIN group to receive 6 days of postoperative supplementation of the polymeric formula (MEIN). Two patients refused to participate in this study, 50 patients underwent other reconstruction procedures (ileocolonic or jejunal reconstruction), and three patients could not receive enteral nutrition after surgery because of postoperative paralytic ileus. These patients were excluded in this study. Among 122 patients, 67 patients who met the eligibility criteria were randomized into an oligomeric formula group (HINE group, $n = 33$) and a polymeric formula group (MEIN group, $n = 34$). Inclusion criteria were: (1) squamous cell carcinoma or adenocarcinoma of the esophagus including Siewert type I/II tumor of

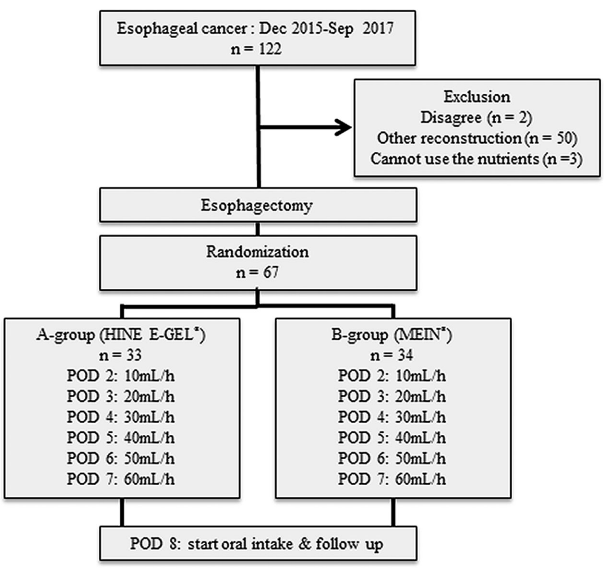

Fig. 1 CONSORT flow chart of the study.

the esophagogastric junction who underwent subtotal esophagectomy and enterostomy; (2) aged 20 years or over; (3) gastric tube reconstruction; and (4) appropriate informed consent. Exclusion criteria were: (1) no enterostomy; (2) a reconstruction procedure different from gastric tube reconstruction; (3) history of digestive surgery (except appendectomy); (4) simultaneous colonic or other digestive surgery; (5) milk, soy, or gelatin allergy; (6) patients with a tendency for loose stool before surgery (defecation frequency of 6 or more times per day).

Random assignment

The patients were randomly assigned either to receive the oligomeric formula (HINE group) or the polymeric formula (MEIN group). Randomization assignment was conducted using a random numbers table. Group sizes were adjusted by age ($<$65 years vs. $\geq$65 years). The randomization arm was revealed to the surgeon after surgery, and then completed the therapy according to the protocol.

Nutrition formulation

MEIN is a form of immunonutrition fortified with whey peptides and the n-3 fatty acids EPA/DHA, exerting postoperative anti-inflammatory, antioxidant, antibacterial, and immune-modulating effects. It contains n-6 and n-3 fatty acids at an n-6: n-3 ratio of 1 : 2. In MEIN, proteins, fat, carbohydrates, and dietary fiber supply 20%, 25%, 52.4%, and 2.6% of energy, respectively. In HINE E-GEL, a milk protein-free (soy peptide and collagen peptide) oligomeric formula with low osmotic load, proteins, fat, carbohydrates, and dietary fibers supply similar percentages of energy as above, more precisely, 16%, 20%, 58.7%, and 5.3% of energy, respectively. HINE E-GEL is designed to be absorbed at higher efficiency, and contains n-6 and n-3 fatty acids at a n-6:n-3 ratio of 1:3; medium chain triglycerides account for 34% of total fat.

Preoperative treatment

Of the 67 patients, 29 had received neoadjuvant chemotherapy, 6 had received neoadjuvant chemoradiotherapy, 8 had received definitive chemoradiotherapy, 17 underwent surgery only, and 7 had received endoscopic submucosal dissection for mucosal or submucosal esophageal cancer. Chemotherapy regimens were 800 mg/m^2 5-fluorouracil [5FU] + 80 mg/m^2 cisplatin (FP) or 75 mg/m^2 docetaxel + 75 mg/m^2 cisplatin + 750 mg/m^2 5FU (DCF). The dose of radiation therapy was $>$50 Gy in 8 patients (definitive chemoradiotherapy) and $\leq$50 Gy in 6 patients (neoadjuvant chemoradiotherapy).

Surgical methods

We typically perform esophagectomy with two- or three-field lymph node dissection depending on the degree of progression of the disease and surgical risk involved. The thoracic approach is by video-assisted thoracoscopic surgery or thoracotomy, and the abdominal approach is hand-assisted laparoscopic surgery or open laparotomy depending on the case. The thoracoscopic approach involves insertion of 5-mm and 12-mm ports through the second and fourth intercostal spaces at the anterior axillary line (assistant's ports) and 11-mm ports through the fifth intercostal space at the mid-axillary line (camera port) and other two ports in the fourth (5 mm) and sixth (11 mm) intercostal spaces at the posterior axillary line (operator's ports). We preserve the thoracic duct in cases with clinical stage (cStage) I and perform resection in cases with cStage $\geq$ II based on the UICC TNM grading system, 7th edition.[11] In this study, the reconstruction technique was gastric tube reconstruction. We inserted jejunostomy tube from the point near the lower end of the gastric tube or the anterior wall of the duodenal bulb to jejunum for all patients in this study.

Posttreatment follow-up management

Posttreatment follow-up was performed by clinical examination, tumor marker testing, enhanced computed tomography scan, intraesophageal endoscopic examination with optional biopsy, and ultrasonography (abdominal and neck) every 4 months for the first 3 years and then every 6 months. Thereafter, a new follow-up period was determined on the basis of the individual risk and likelihood of recurrence.

Nutritional assessment

Nutritional status was assessed using the Prognostic Nutritional Index (PNI) and the Controlling Nutritional Status (CONUT) score. PNI was calculated by using the following formula: PNI = (10 × serum albumin concentration [Alb]) + (0.005 × peripheral total lymphocyte count [TLC]). As shown in Table 1, the CONUT score, an indicator of protein and lipid metabolism and immunity, was calculated using the Alb, TLC, and total cholesterol (TC) values,[13] and used for malnutrition screening in 4 grades (normal, mild, intermediate, and severe). Blood tests were performed to determine TLC, total protein (TP), albumin (Alb), total cholesterol, pre-Alb, C-reactive protein (CRP), and zinc (Zn). Changes in body weight, skeletal muscle mass, body fat percentage, and body mass index (BMI) were also measured using a Body Composition Analyzer (INBODY720®; Biospace Co., Ltd., Seoul, Korea). The rate of change in rapid turnover proteins (pre-Alb,

Table 1 Assessment of the screening tool for CONUT score.

	Parameter			
	Normal	Mild	Moderate	Severe
Serum albumin (g/dL)	≥3.50	3.49–3.00	2.99–2.50	<2.5
(Score)	(0)	(2)	(4)	(6)
Total lymphocyte count (/μL)	≥1600	1599–1200	1199–800	<800
(Score)	(0)	(1)	(2)	(3)
Total cholesterol (mg/dL)	≥180	179–140	139–100	<100
(Score)	(0)	(1)	(2)	(3)
	Interpretation			
Total CONUT score	0–1	2–4	5–8	9–12
Malnutrition status	Normal	Mild	Moderate	Severe

CONUT, controlling nutritional status.

retinol-binding protein (RBP), and transferrin) and skeletal muscle mass was calculated by using the following formula: (Rate of change in these parameters) (%) = [(Postoperative parameters)—(Preoperative parameters)]/Preoperative parameters × 100. All items above were measured before surgery, and at 14 days, 1 month, 3 months, and 6 months after surgery; data were compared between the HINE group and MEIN group.

Sample size

The projected frequency of diarrhea for HINE-group and MEIN-group patients was 10% and 25%, respectively, from our experience, and we initially planned to recruit 200 patients (100 each group) to detect this difference with double-sided α-error of 0.05 and statistical power of 80%. Recruitment was slow and we thought that the frequency of diarrhea for MEIN group may be higher than anticipated in an intermediate analysis. Thus, the Institutional Review Board of Toranomon Hospital approved an amendment to change the number of patients. Finally, the projected frequency of diarrhea for HINE-group and MEIN-group patients was 10% and 40%, respectively, and we planned to recruit 64 patients (32 per group) to detect this difference with double-sided α-error of 0.05 and statistical power of 80%.

Statistical analysis

Pairwise differences of proportions and medians were analyzed by using a chi-square test, Fisher's exact test, or Mann–Whitney U test as appropriate. For all analyses, differences were considered statistically significant when $P < 0.05$. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 19.0J for Windows (SPSS Inc., Chicago, IL).

RESULTS

Patient characteristics

Table 2 summarizes the patient characteristics of the two groups. Both groups were similar with respect to age (≥65 and <65 years), sex, BMI, performance status (PS), clinical T factor, clinical N factor, clinical stage, tumor localization, content of preoperative treatment, extent of lymph node dissection, operative approach (thoracic/abdominal), resection/preservation of the thoracic duct, reconstruction route, and the amount of bleeding. The operative duration was significantly longer in MEIN group than in HINE group (575.5 vs. 541.0 min, respectively; $P = 0.006$).

Postoperative complications

Table 3 summarizes the postoperative complications of the two groups. Clavien-Dindo classification grade ≥2 events were documented as complications. Postoperative complications were found in 15 patients, 45.5% (17 complications) in the HINE group and in 16 patients, 45.7 % (16 complications) in the MEIN group, with no significant difference between the groups ($P = 0.895$). No significant difference was also found in the incidence of anastomotic leakage, pneumonia, pleural effusion, cervical lymphorrhea, postoperative bleeding, chylothorax, and other complications (e.g. anastomotic stenosis and bilateral recurrent nerve paralysis). No deaths occurred in either group. No significant difference was also observed in the incidence of CD grade ≥3 complications, which occurred in 11 (33.3 %) patients in HINE group and 11 (32.4 %) patients in MEIN group ($P = 0.932$). However there might have been significant difference in the original setting of the study with 200 patients (100 each group).

Postoperative short-term outcomes

Table 4 showed the postoperative short-term outcomes. Both groups were similar with respect to the length of postoperative ICU stay and the length of

Table 2 Patient characteristics.

	A group: HINE ($n = 33$)	B group: MEIN ($n = 34$)	p-value
Age (≥65/<65)	17/16	20/14	0.548
Sex (male/female)	27/6	30/4	0.155
BMI (kg/m^2)	21.9 (15.0–26.9)	21.5 (15.2–27.8)	0.490
Performance status			
0	27	30	0.461
1	6	4	
c T factor (7th)			
1a/b	2/10	2/11	0.664
2	4	8	
3	14	10	
4a/b	0/3	1/2	
c N factor (7th)			
0	11	14	0.171
1	15	8	
2	7	10	
3	0	2	
c Stage (7th)			
IA/IB	9/0	9/2	0.593
IIA/IIB	2/5	2/4	
IIIA/IIIB/IIIC	9/3/0	7/2/3	
IV	5	5	
Tumor localization			
Ce	1	1	0.546
Ut	4	9	
Mt	18	16	
Lt	8	4	
Ae	1	2	
EGJ	1	2	
Preoperative treatment			
NACT	15	14	0.994
NACRT	3	3	
DCRT	4	4	
ESD	3	4	
None (surgery only)	8	9	
Lymphadenectomy			
D2/D3	7/26	4/30	0.297
Operative approach (thoracic)			0.461
Open	6	4	
VATS	27	30	
Operative approach (abdomen)			
Open	10	11	0.856
HALS	23	23	
Thoracic duct			
Preservation	7	8	0.820
Resection	26	26	
Reconstruction route			
Retrosternal	30	32	0.617
Posterior mediastinal	3	2	
Operative duration (min)	541.0 (270–628)	575.5 (435–764)	0.271
Amount of bleeding (mL)	282.0 (50–1004)	392.5 (42–1363)	0.192

postoperative hospital stay. No significant difference was also found in average defecation frequency. The rate of antiflatulent (MIYA-BM®; Miyarisan pharmaceutical Co., Ltd., Tokyo, Japan) use in the MEIN group (29.4%) tended to be higher than in the HINE group (12.1%), albeit not significantly ($P = 0.082$). On the other hand, the rate of diarrhea, defined as Bristol scale types 6 and 7, was significantly lower in the HINE group than in the MEIN group (18.2% vs. 64.7%, $P < 0.001$). Figure 2 shows the rate of each stool form using Bristol scale between two groups from POD1 to POD7. There are no significant differences between the two groups from POD1to POD4. The score of Bristol scale of POD5 tended to be lower in the HINE group ($P = 0.086$), and these score of POD6 and POD7 was significantly lower in the HINE group ($P = 0.019$ and $P = 0.006$, respectively). Also, the completion rate of enteral nutrition was significantly higher in the HINE group than in the MEIN group (97.4% vs. 86.6%, respectively; $P = 0.002$). No significant difference was observed in the median dietary intake of calories after surgery ($P = 0.668$).

Table 3 Postoperative complications.

	A group: HINE ($n = 33$)	B group: MEIN ($n = 34$)	p-value
Morbidity (CD Grade II-)	15	16	0.895
Morbidity (CD Grade III-)	11	11	0.932
Pneumonia(Grade II)	2	3	0.667
Pleural effusion	1	0	0.307
Anastomotic leakage	6	4	0.461
Postoperative bleeding	1	2	0.573
Chylothorax	3	1	0.288
Cervical lymphorrhea	2	3	0.667
Other (anastomotic stenosis, bilateral recurrent nerve paralysis)	2	3	0.667

Table 4 Postoperative outcomes.

	A group: HINE ($n = 33$)	B group: MEIN ($n = 34$)	p-value
Postoperative ICU stay (days)	3.0 (2–5)	3.0 (1–8)	0.560
Postoperative hospital stay (days)	27.0 (14–77)	26.5 (15–158)	0.692
Diarrhea (Bristol Stool Form Scale)			< 0.001
Types 1–5	27	12	
Types 6,7	6	22	
Average defecation frequency (/day)	0.871 (0–2)	0.973 (0–4)	0.612
Use of antiflatulents	4 (12.1%)	10 (29.4%)	0.082
Completion rate of enteral nutrition regimen (%)	97.4 (42.9–100)	86.6 (42.9–100)	0.002
Dietary intake calories (kcal/day)	1900.0 (1500–2500)	1868.8 (1300–2500)	0.668

Nutritional status

Median follow-up was 16.3 (6.4-29.7) months in the HINE group and 16.5 (5.7–29.9) months in the MEIN group ($P = 0.826$; Kaplan–Meier estimate). Figure 3a shows changes in CONUT score. CONUT scores at 6 months after surgery were significantly lower in the HINE group than in the MEIN group ($P = 0.030$), indicating improved tendency in nutritional status in the HINE group. There were no significant differences in CONUT score at any other time points. No significant differences in PNI were seen between the two groups (Fig. 3b). Figure 4a shows time trends in blood test data. Chronological changes were minimal in TLC, and levels of Alb, CRP, and Zn throughout the 6-month observation period. But TP levels at 6 months after surgery were significantly higher in the HINE group than in the MEIN group ($P = 0.023$). The rates of change in rapid turnover protein (pre-Alb, RBP, and transferrin) levels as short-term nutritional status did not differ significantly at any time points (Fig. 4b). There were no significant differences in ferrokinetics between the two groups (Fig. 4c).

Figure 5 shows changes in body composition. There were no differences in changes in body weight, BMI, and body fat percentage between the groups. The rate of change in skeletal muscle mass from preoperative levels decreased until 3 months after surgery, but reverted 6 months after surgery in both groups. And no significant difference was also observed in this parameter.

DISCUSSION

This study compared completion rates of the enteral nutrition regimen, frequency of diarrhea and, short-term and long-term nutritional status between an oligomeric formula HINE E-GEL and a polymeric immuno-nutrition MEIN to determine the optimum enteral nutrition formula that imposes less burden on patients following esophageal cancer surgery. This study showed that HINE E-GEL, compared with MEIN, had less tendency to induce the frequency of diarrhea, enabling more patients to adhere to the postoperative enteral nutrition plan. Furthermore, short-term and long-term maintenance of nutritional status with HINE E-GEL was comparable or potentially better in some nutrition indicators to that with the immuno-nutrition formula MEIN.

The postoperative frequency of diarrhea judged by the Bristol stool scale was significantly lower in patients who received HINE E-GEL, and this was accompanied by a higher completion rate of the enteral nutrition regimen. Previously proposed causes of enteral nutrition-related diarrhea include high caloric density, feeding rate, temperature of the enteral nutrition product use, bacterial growth, and

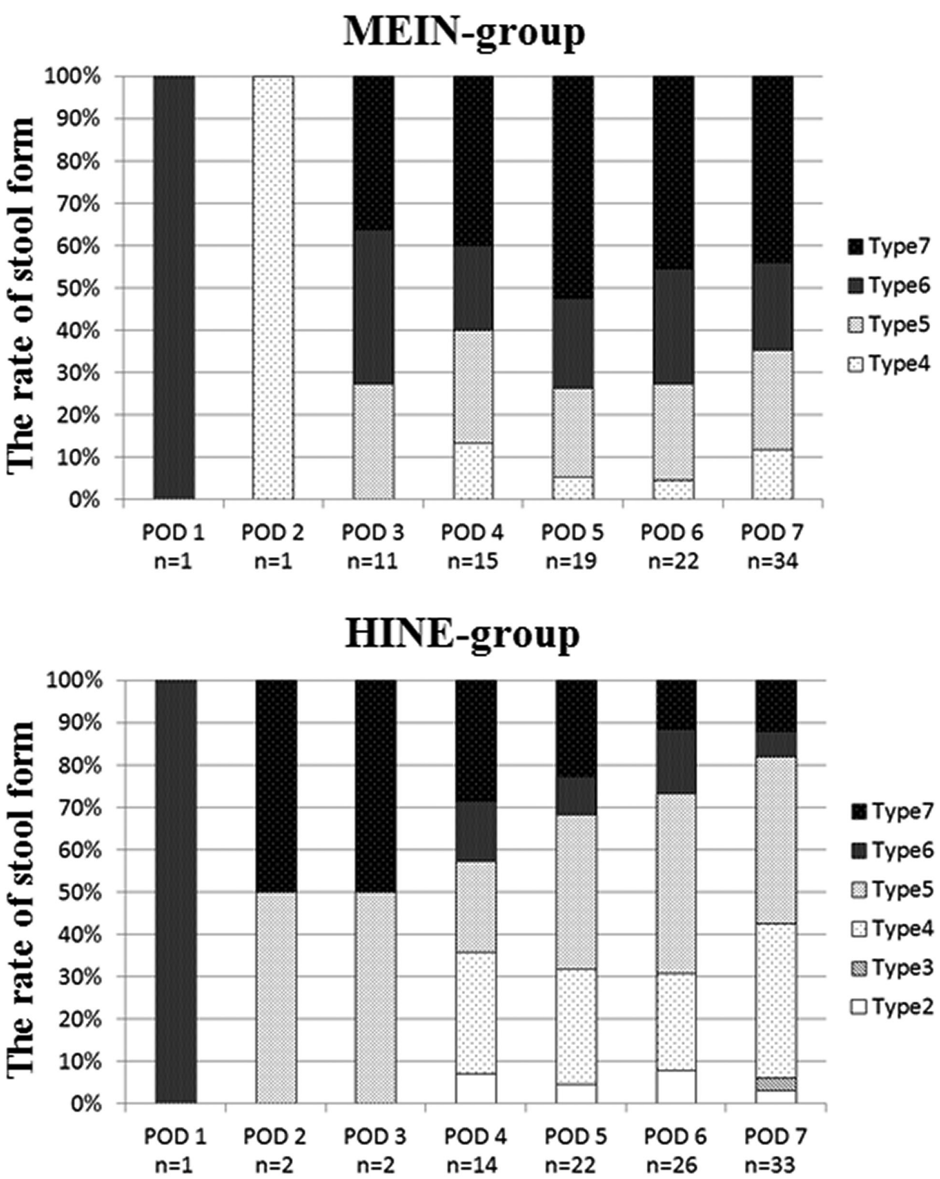

Fig. 2 The rate of each stool form using Bristol scale between two groups from POD 1 to POD 7.

the presence/absence of dietary fiber components.[14] There were no differences in feeding rate, temperature of the enteral nutrition products used, and the possibility of bacterial growth between HINE E-GEL and MEIN in this study. HINE E-GEL has a lower osmotic pressure (360 /L vs. 600 mOsm/L) and caloric density (0.8 vs. 1.0 kcal/mL) than MEIN, and this may explain the difference in the postoperative frequency of diarrhea between the two groups in this study.

Another possible cause is the dietary fiber content. HINE E-GEL contains less dietary fiber (2.2 g/200 mL) than MEIN (3.6 g/200 mL). However, composition of dietary fiber, but not the content, may be the reason for less frequent diarrhea in patients who received HINE E-GEL. Nutrient formula including MEIN usually contains indigestible dextrin, while HINE E-GEL contains pectin purified from plants (0.9 g/100 kcal). Generally, enteral feeding with soluble fiber reduced the incidence of diarrhea, on the other hand, insoluble fiber is said to cause diarrhea.[15] Pectin and indigestible dextrin are both soluble fiber. Pectin is slightly costly, but has a good intestinal conditioning action and anti-diarrheal effect, as shown in the study by Schultz *et al.*[16] The pectin is a high-molecular weight (about 50,000–360,000) polysaccharide, which may form a matrix of the food, delaying digestion, and colonic transit time.[17,18] Of these mechanisms, HINE E-GEL, compared with MEIN, could reduce the frequency of diarrhea.

The polymeric formula contains nitrogen in form of whole proteins and needs the digestion process with the gastrointestinal tract. On the other hand, the nitrogen sources of oligomeric formula are proteins that have been hydrolyzed into oligopeptides of varying lengths, dipeptides, and tripeptides. These

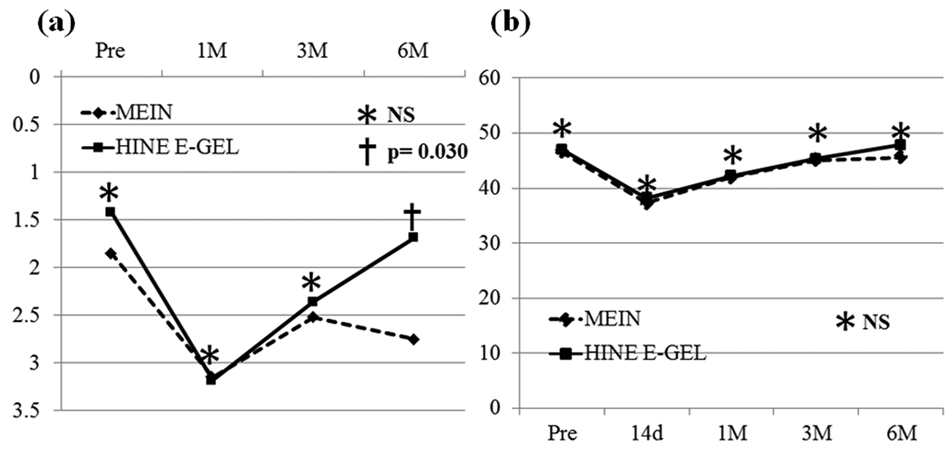

Fig. 3 (a) CONUT score; (b) Prognostic Nutritional Index.

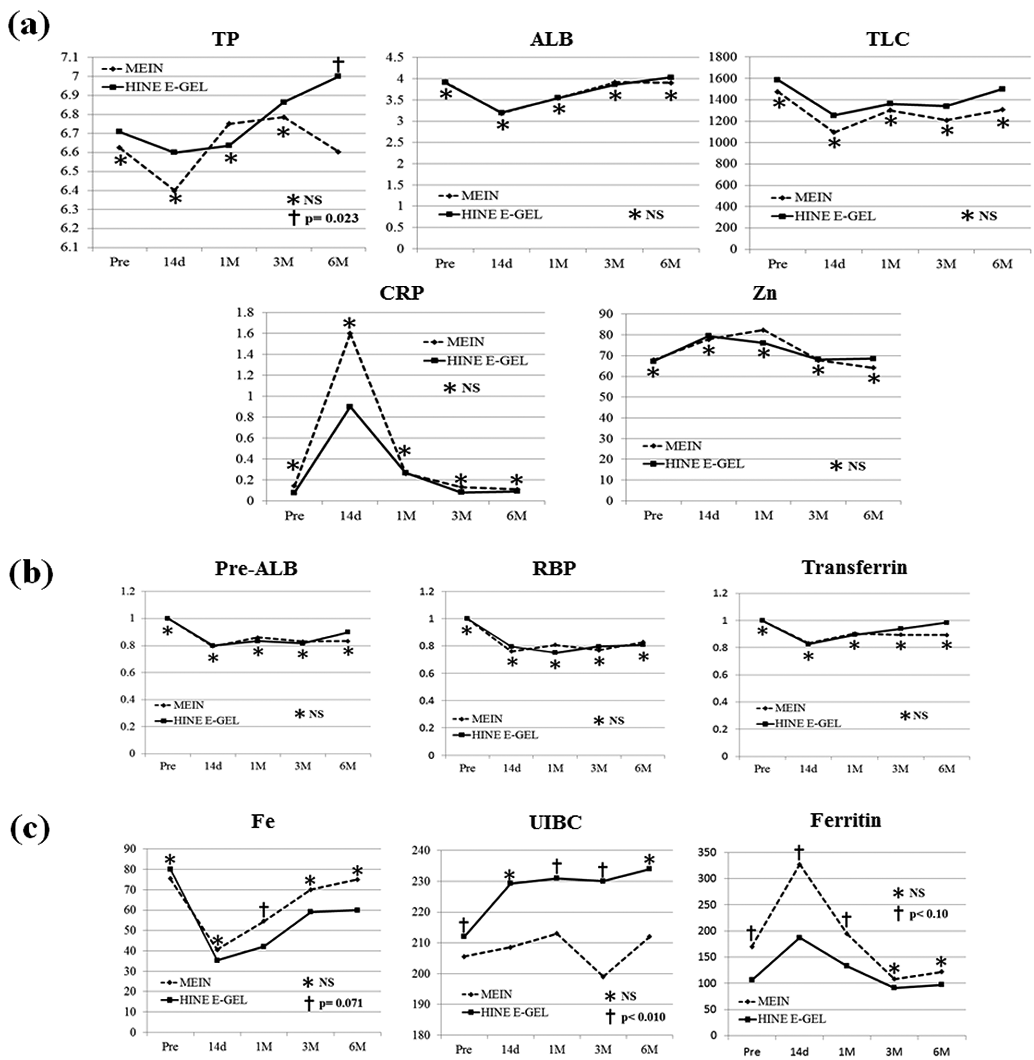

Fig. 4 (a) Time trends in blood test data; (b) The rate of change in rapid turnover proteins; (c) Time trends in ferrokinetics.

peptides of oligomeric formulas have specific uptake transport mechanisms and are thought to be absorbed more efficiently than whole proteins.[19] Given impaired digestive function in esophageal cancer patients following digestive system surgery, oligomeric and monomeric (elemental) formulas place less burden on the digestive system and are absorbed better, and thus are thought to be more favorable options compared with polymeric formulas including MEIN. Besides, while the protein source of MEIN is milk, that of

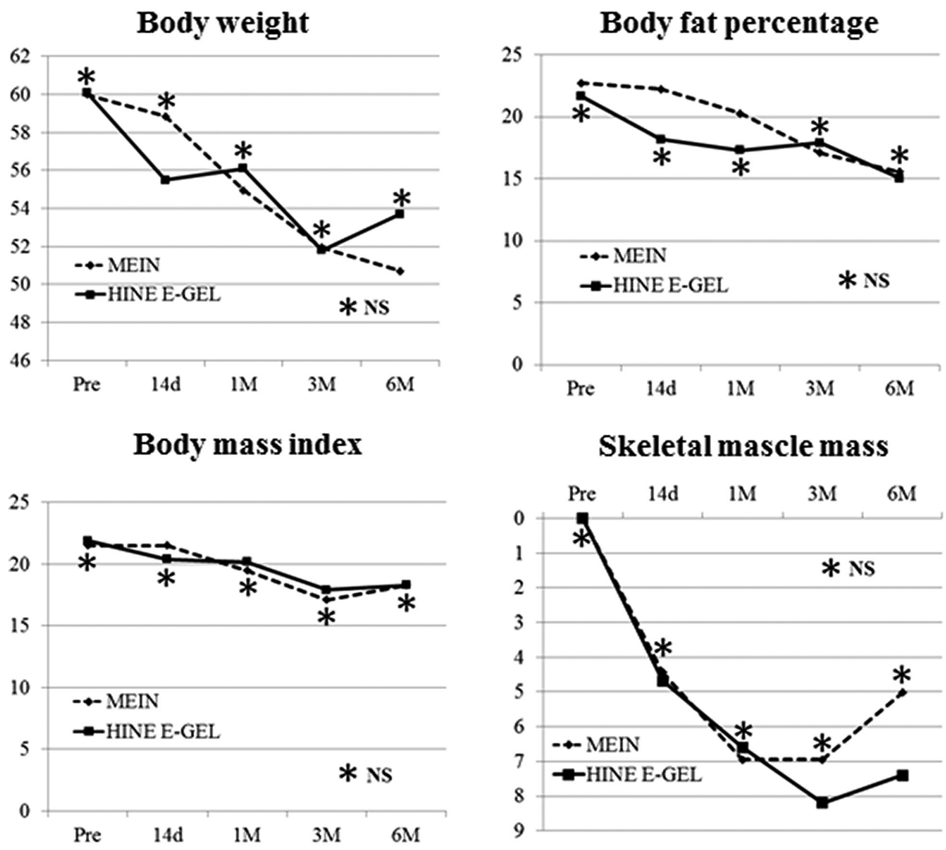

Fig. 5 Changes in body composition.

HINE E-GEL is non-milk (soy peptide and collagen peptide). Generally speaking, about 65% of people show some form of lactose intolerance. It is well known that there are significant differences in this phenomenon among populations and regions. In East Asia, it is said that more than 90% of adults had lactose intolerance.[20] The source of protein may be another reason for less frequent diarrhea in patients who received HINE E-GEL in our study. Such favorable outcomes of HINE E-GEL of low frequency of diarrhea and high completion rate of enteral nutrition regimen might explain to some extent the better results of rapid turnover protein levels as short-term nutritional status or better CONUT score or TP levels as long-term nutritional status at 6 months after surgery to that with the immunonutrition formula MEIN despite the small total calorie intake. However, we think it difficult to conclude directly that the statistical differences shown in the long-term nutritional status can be explained only by the kind of the nutrients, but other factors such as tumor stage, postoperative complications, patients body composition, and some other unknown causes might have existed in this study with small sample size.

The major limitations of this study were its single-center examined and small sample size. An external validation study or a multicenter study with a larger number of cases would be needed to confirm the current observations.

CONCLUSIONS

Use of an oligomeric formula HINE E-GEL, as an alternative to MEIN, reduced the frequency of diarrhea. Furthermore, nutritional status maintained with HINE E-GEL was comparable or potentially better in some nutrition components to that with the immunonutrition formula MEIN, indicating that HINE E-GEL can be an option for enteral nutrition following esophageal surgery to achieve the goal of successful completion of scheduled enteral nutrition and smooth transition to the normal diet.

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