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ORIGINAL ARTICLE

A randomized controlled trial comparing antioxidant-enriched enteral nutrition with immune-enhancing enteral nutrition after esophagectomy for cancer: a pilot study

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Abstract
Purpose The objective of this study was to compare the effects of two types of enteral supplements, an antioxidant-enriched enteral nutrition (AeEN) and an immune-enhancing enteral nutrition (IeEN), on the nutrition, immunoinflammatory response, antioxidant capacity and clinical outcomes in patients after esophagectomy for cancer.
Methods Patients ($n = 20$) undergoing esophagectomy for cancer were randomized in this single-center, open-label study. Two types of enteral supplements were used for 5 days before surgery and 7 days after surgery. The circulating levels of nutritional markers, immunoinflammatory markers, oxidative stress markers, and the antioxidant capacity were compared throughout the perioperative period, and the patients' clinical outcomes were also compared.
Results The circulating levels of nutritional markers decreased after surgery, but the changes were not significantly different between the AeEN group and the IeEN group throughout the perioperative period. Surgery increased the immunoinflammatory markers, and the levels were not significantly different between the groups after surgery. Surgery also increased the levels of oxidative stress markers, but there were no significant differences between the groups throughout the study period.
Conclusions The results of this pilot study suggest that AeEN and IeEN have a similar effect on nutrition, the immunoinflammatory response, antioxidant capacity and clinical outcomes after esophagectomy for cancer. These findings, therefore, warrant further studies on a larger scale.

Keywords Antioxidant-enhancing enteral nutrition · Immune-enhancing enteral nutrition · Esophagectomy for cancer · Randomized controlled trial

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Introduction

In the past 10 years, there have been many reports concerning the efficacy of immune-enhancing nutrients (IeNs) including arginine, omega-3-unsaturated fatty acids, nucleotides and other molecules used prior to gastrointestinal surgery [1–4]. The immune-enhancing enteral nutrition (IeEN) is considered to increase the immune response and improve the surgical outcomes such as mortality and morbidity, the length of the intensive care unit (ICU) stay, the length of the hospital stay, and other outcomes. Impact® includes supplemental arginine, omega-3-unsaturated fatty acids, nucleotides, and is specialized as IeEN. We have previously reported a retrospective study that showed that the Impact® IeEN reduced the duration of systemic inflammatory response syndrome (SIRS) and the morbidity after esophagectomy for cancer [5]. According to the consensus recommendations of the American Society for Parenteral and Enteral Nutrition (ASPEN), the preoperative use of IeEN offers a benefit for patients undergoing elective gastrointestinal surgery such as esophagectomy [6]. In the guidelines on enteral nutrition of the European Society for Clinical Nutrition and Metabolism (ESPEN), the perioperative management is focused on

the enhanced recovery of patients after surgery (ERAS). According to those guidelines, the preoperative use of enteral nutrition including immunomodulatory substances is recommended for cancer patients undergoing major upper abdominal surgery [7].

A variety of diseases are recognized to be related to oxidative stress resulting from an imbalance between oxidants produced by various stresses and the natural antioxidant capacity. The overproduction of reactive oxygen species (ROS) arising from inflammation due to stresses such as surgery, trauma, burns and other causes, as well as in life-style-related diseases, can cause damage to cells. Accordingly, it is hoped that antioxidants can reduce the oxidative stress and the subsequent organ damage [8]. There was a report that indicated that antioxidant-enriched enteral nutrition (AeEN) increased the immune response in patients undergoing major gastrointestinal surgery [9]. In contrast, there was another report that the AeEN including glutamine and an antioxidant solution did not improve the prognoses of burned and major trauma patients [10], and that AeEN including an antioxidant, and vitamins A, C, and E improved the blood level of antioxidants, but did not improve the clinical outcomes [11]. The Anom® AeEN includes antioxidants such as catechin and proanthocyanidin. It also includes arginine, omega-3-polyunsaturated fatty acids and nucleotides.

The purpose of this prospective randomized trial was to compare the effects of AeEN (Anom®) and IeEN (Impact®) on the nutritional markers, immunoinflammatory markers, antioxidant capacity and clinical outcomes in patients undergoing esophagectomy for cancer.

Methods

During the period from June 2007 to June 2009, 20 patients were enrolled in this trial who met the following conditions: (1) younger than 75 years of age, (2) potentially resectable esophageal cancer of clinical stage II–III, (3) no pretreatment, (4) possible peroral intake, (5) proposed operation being right-sided transthoracic esophagectomy and esophageal reconstruction using a gastric conduit, and (6) the informed consent provided. They were randomly divided into two groups: an of AeEN group that received Anom® an IeEN group that received Impact®. The elements per 100 ml of Anom® and Impact® are described in Table 1. Both formulas included the basic nutrients such as protein, fat and carbohydrates. They both also contained immune-enhancing nutrients such as arginine, omega-3-polyunsaturated fatty acids and nucleotides. However, the levels of such nutrients were much higher in the Impact® than in the Anom® supplement. On the other hand, glutamine and antioxidants, such as catechin and proanthocyanidin, were included in the Anom®, but not in the Impact® supplement.

Table 1 Contents per 100 ml

	AeEN (Anom®)	IeEN (Impact®)
Calorie (Kcal)	100	100
Protein (g)	5.0	5.6
Arginine (g)	0.46	1.28
Glutamine (g)	0.75	–
Fat (g)	2.8	2.8
ω3/ω6[a]	0.5	1.3
Carbohydrate (g)	14.0	13.4
Vitamins		
C (mg)	100	9.5
E (mg)	5.0	0.67
Others	A, B_1, B_2, B_6, B_{12}, D, K_2, niacin, pantothenic acid, folic acid	
Minerals		
Zn (mg)	1.5	0.67
Cu (mg)	0.15	0.12
Se (μg)	5.0	3.3
Cr (μg)	6.0	2.0
Others	Na, Cl, K, Ca, Mg, P, Fe, I, Mn	
Nucleotide (g)	0.013	0.129
Antioxidant (mg)		
Catechin (polyphenol)	35	
Proanthocyanidin	20	

[a] Ratio of the omega-3-polyunsaturated fatty acid to the omega-6-polyunsaturated fatty acid

Both nutrient supplements were administered according to the standard Clinical Pathway (Fig. 1). In the AeEN group, 800 ml of Anom® was given perorally for 5 days before surgery at a total dose of 4,000 ml, while in the IeEN group, 750–1,000 ml of Impact® were given perorally for 5 days before surgery for a total dose of 4,000 ml. For 7 days after surgery, Anom® (from 400 to 1,600 ml) was given using a gastrostomy at a total dose of 8,400 ml, while in the IeEN group, Impact® (from 500 to 1,500 ml) was given using a gastrostomy for a total dose of 8,500 ml. All the protocols were approved by the institutional review board of the Kurume University School of Medicine (#06058: 29 September 2006), and all the patients provided informed consent for their participation in this trial.

The patients' demographic information such as their age, gender, body weight and body mass index (BMI) on admission, diet on admission, co-morbidities, the clinical and pathological TNM stages (UICC 7th ed.) [12], surgical procedures, and the length of the operation and blood loss were not significantly different between the AeEN group and the IeEN group (Tables 2, 3). All the patients underwent right-sided transthoracic esophagectomy with

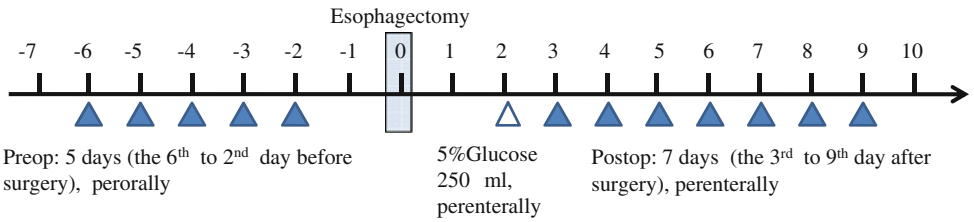


Fig. 1 The dosing protocol for the enteral supplements. The AeEN (Anom®) group: 4,000 ml (800 ml/day × 5 days) before surgery + 8,400 ml (400–1,600 ml/day) after surgery. The IeEN (Impact®) group: 4,000 ml (750 ml/day × 4 days + 1,000 ml/day × 1 day) + 8,500 ml (500–1,500 ml/day) after surgery

Table 2 Patients' background

	AeEN (Anom®) $n = 10$	IeEN (Impact®) $n = 10$	p value
Age	67 ± 5	65 ± 7	ns
Sex (male:female)	8:2	10:0	ns
Body weight (kg)[a]	55 ± 11	58 ± 8	ns
Body mass index[a]	21.1 ± 3.3	21.1 ± 3.3	ns
Diet			
Normal/gruel/liquid	9/0/1	7/1/2	ns
Co-morbidities			
Pulmonary diseases[b]	1	0	ns
Liver dysfunction[c]	3	4	ns
Diabetes mellitus[d]	1	2	ns
Cardiac diseases	0	1[e]	ns
Clinical T-stage			
cT1/T2/T3/T4	3/0/7/0	2/0/8/0	ns
Clinical N-stage			
cN0/N1/N2/N3	2/3/4/1	3/2/4/1	ns
Clinical M-stage			
cM0/M1-Lym	10/0	7/3	ns
Clinical stage			
c stage I/II/III/IV	2/1/7/0	2/1/4/3	ns
Pathological T-stage			
pT 1/T2/T3/T4a/T4b	3/1/5/1/0	2/1/4/2/1	ns
Pathological N-stage			
pN0/N1/N2/N3	3/2/3/2	6/0/2/2	ns
Pathological M-stage			
pM0/M1-Lym	10/0	8/2	ns
Pathological stage			
pStage I/II/III/IV	3/1/6/0	2/2/4/2	ns
Residual tumor			
R0/R1	10/0	8/2	ns

ns no significant difference

[a] On admission

[b] Chronic obstructive pulmonary diseases ($FEV_{1.0} < 2{,}000$ ml)

[c] Chronic viral hepatitis or alcoholic liver disease assessed as grade II or more with ^{99m}Tc-GSA scintigraphy

[d] Diabetes requiring medication

[e] Atrial fibrillation

thoracoabdominal two-field or cervicothoracoabdominal three-field lymphadenectomy, followed by esophageal reconstruction using a gastric conduit. The route of esophageal reconstruction was a retrosternal route in one patient and a subcutaneous route in the other nine patients in the AeEN group, while it was a subcutaneous route in all ten patients in the IeEN group. None of the patients underwent a perioperative blood transfusion, although all of the patients had autotransfusions of 800 ml prepared in case a transfusion was necessary. Enteral nutrition was not discontinued in any patient, although abdominal distension was observed in two patients in the IeEN group.

The patients' body weight and the BMI were measured 7 and 1 day before surgery, and on the first, third, seventh and thirteenth days after surgery. As nutritional markers, the levels of serum protein, albumin, transferrin and retinol

Table 3 Surgical procedures and perioperative outcomes

	AeEN (Anom®) $n = 10$	IeEN (Impact®) $n = 10$	p value
Approach[a]			
Thoracoscopic/open	2/8	2/8	ns
Lymphadenectomy			
2-field/3-field	3/7	0/10	ns
Route of esophageal reconstruction[b]			
Subcutaneous/retrosternal	9/1	10/0	ns
Operating duration (min)	612 ± 90	585 ± 80	ns
Bleeding amount (g)[c]	466 ± 353	405 ± 167	ns
SIRS (days)			
Mean	1.8 ± 1.5	3.4 ± 3.5	ns
Median	1	1	ns
Hospital stay			
Mean	39.6 ± 15.0	41.2 ± 12.0	ns
Median	35	38	ns
Postoperative complications	4 (40 %)	4 (40 %)	ns
Anastomotic leak[d]	3 (30 %)	3 (30 %)	ns
SSI	3 (30 %)	1 (10 %)	ns
Pulmonary complication	0	1 (10 %)[e]	ns

ns no significant difference, *SIRS* systemic inflammatory response syndrome, *SSI* surgical site infection

[a] Transthoracic esophagectomy (TTE)

[b] Gastric conduit

[c] No patient received blood transfusion perioperatively

[d] Minor leak spontaneously healed

[e] Aspiration pneumonia requiring mini-cricothyroidotomy

binding protein (RBP) were measured 7 and 1 day before surgery and on the seventh and thirteenth days after surgery. As immunoinflammatory markers, the WBC, C-reactive protein (CRP), interleukin-6 (IL-6) and interleukin-8 (IL-8) levels were measured. The WBC and CRP level were measured 7 and 1 day before surgery and days after surgery. IL-6 and IL-8 were measured immediately and on the first and second days after surgery. As oxidative stress markers, the urinary levels of 8-hydroxy-2′-deoxyguanosine (8OHdG), an oxidized nucleotide, and 8-isoprostane, an oxidized lipid, were measured, and the potential antioxidant (PAO) level in the serum was measured as an indicator of the antioxidant capacity. These three parameters were measured 7 and 1 day before surgery and on the second and thirteenth days after surgery.

The incidence of postoperative complications, the length of SIRS, the length of hospital stay, nutritional markers, immunoinflammatory markers and the antioxidant capacity were compared between the two groups. SIRS was defined as fulfilling at least two of the following four conditions; (1) body temperature >38 °C or <36 °C, (2) pulse >90/min, (3) respiration >20/min, $PaCO_2 < 32$ mmHg or need for assisted ventilation, (4) WBC > 12,000/mm^3 or <4,000/mm^3. The length of hospital stay was defined as the duration until the initiation of postoperative chemotherapy and/or radiotherapy in patients receiving adjuvant therapy.

The Wilcoxon–Mann–Whitney test was used to examine the differences between the AeEN group and the IeEN group at the initial time point of measurements with a 5 % level of significance. The difference between the two groups after the initial time point was analyzed by examining the $\beta 2$ in the following model that was adjusted for the difference in the measurements at the previous time point.

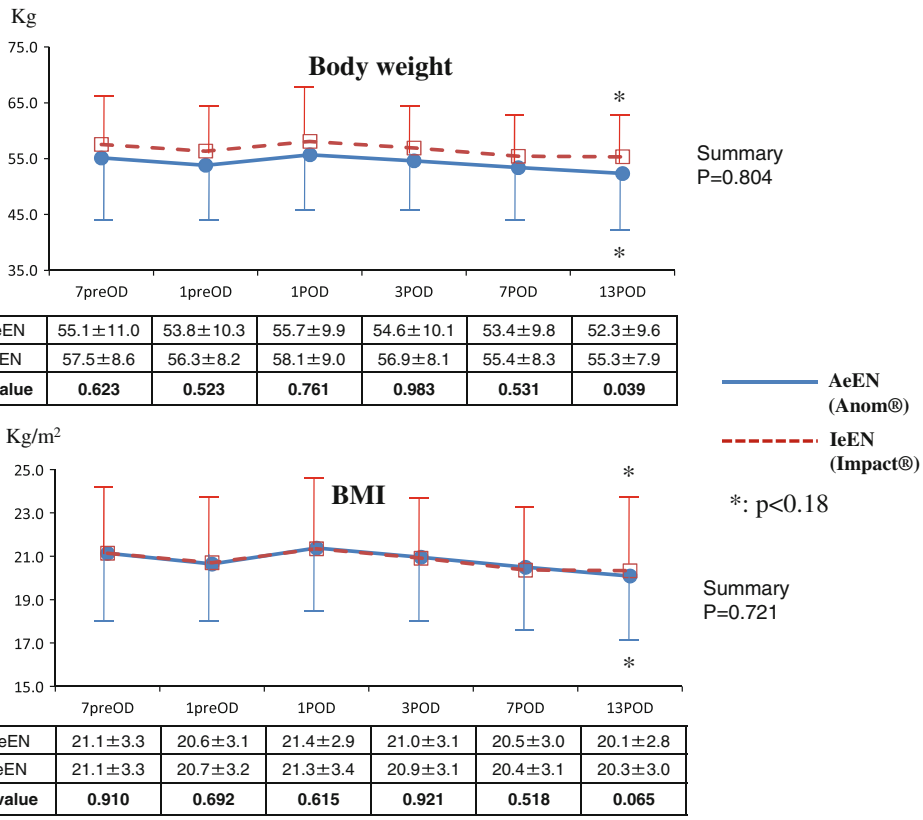
$$y = \beta 0 + \beta 1\ (\text{the previous value}) + \beta 2\ (\text{group}) + \gamma\ (\text{the previous value})\ (\text{group})$$

The p values at several time points after the initial measurement were summarized using summary statistics which were constructed by adding $\beta 2$ at those time points. Since the absolute sizes of the two groups were fairly small for conventional statistical tests with a 5 % level of significance, the Akaike Information Criterion (AIC) which chose the most reasonable model based on the Kullback–Leibler Information [13] was employed except for the test at the initial point; this was determined by simple computation to indicate the equivalence of the two groups if the p value was >0.18 and no equivalence if the p value was <0.18.

Results

The changes in the body weight and the BMI are shown in Fig. 2. Both values were increased for several days after surgery and decreased to the preoperative level within a week. No differences were observed in the perioperative changes in the body weight and BMI between the two groups, except for the thirteenth day after surgery when they were higher in the IeEN group.

The changes in the nutritional markers such as protein, albumin, transferrin and RBP levels appear were in Fig. 3. The levels of the nutritional markers were increased by the



	7preOD	1preOD	1POD	3POD	7POD	13POD
AeEN	55.1±11.0	53.8±10.3	55.7±9.9	54.6±10.1	53.4±9.8	52.3±9.6
IeEN	57.5±8.6	56.3±8.2	58.1±9.0	56.9±8.1	55.4±8.3	55.3±7.9
P-value	**0.623**	**0.523**	**0.761**	**0.983**	**0.531**	**0.039**

	7preOD	1preOD	1POD	3POD	7POD	13POD
AeEN	21.1±3.3	20.6±3.1	21.4±2.9	21.0±3.1	20.5±3.0	20.1±2.8
IeEN	21.1±3.3	20.7±3.2	21.3±3.4	20.9±3.1	20.4±3.1	20.3±3.0
P-value	**0.910**	**0.692**	**0.615**	**0.921**	**0.518**	**0.065**

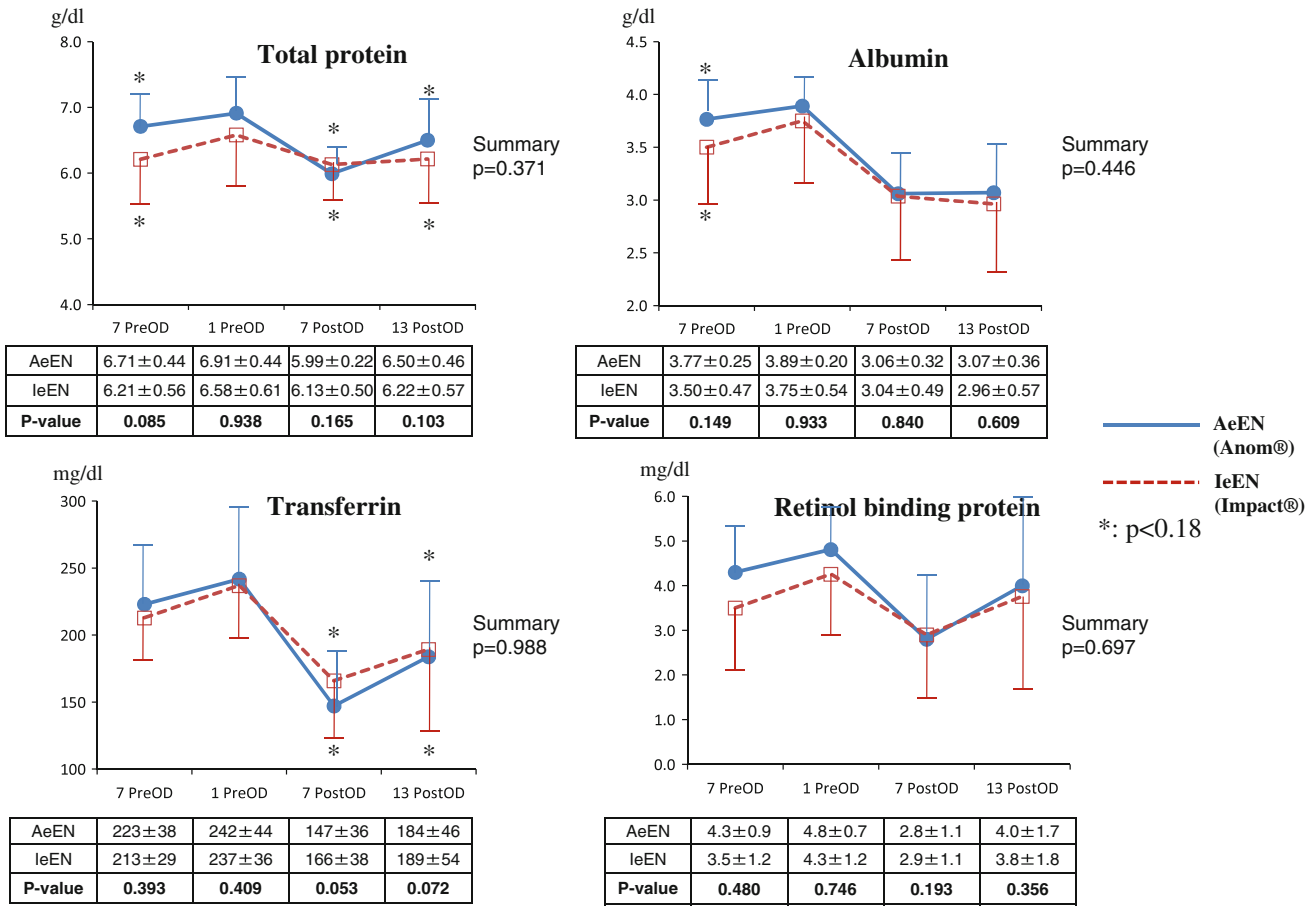
Fig. 2 The perioperative changes in the body weight and body mass index. The initial *p* value was calculated using the Wilcoxon–Mann–Whitney test, and other *p* values, including the summary *p* value, were calculated according to the Akaike Information Criterion. * A statistically significant difference was defined as being less than 0.18 according to the statistical methods employed

preoperative administration of the nutrients for 5 days in both groups, and they decreased after surgery, and then increased again by the postoperative administration of the nutrients for 7 days in the both groups. The total protein level was higher on the seventh day after surgery in the IeEN group, while it was higher on the thirteenth day after surgery in the AeEN group. The transferrin level was higher on both the seventh and thirteenth days after surgery in the IeEN group. However, no significant differences were found overall in any of the four nutritional markers between the groups. In short, no differences were observed in the nutritional markers between the AeEN group and the IeEN group through the period from 7 days before surgery to the thirteenth day after surgery.

Figure 4 shows the changes in immunoinflammatory markers such as the WBC and the CRP, IL-6 and IL-8 levels. All of these markers were increased after surgery; however, IL-6 and IL-8 rapidly decreased by the day after surgery, and the CRP level slowly decreased for 1 or 2 weeks. The WBC remained high for 2 weeks after surgery. The WBC was high in the AeEN group on the first and thirteenth days after surgery, while it was higher in the IeEN group on the seventh day after surgery. The CRP level was higher in the AeEN group on the seventh day after surgery. In addition, overall CRP level was significantly higher in the AeEN group. No significant differences were found in the levels of IL-6 and IL-8 between the groups at any point or overall. In short, only the level of CRP was significantly different between the two groups, being no difference was observed in the inflammatory markers between the AeEN group and the IeEN group throughout the period after surgery, except for CRP which was more reduced in the IeEN.

Figure 5 shows the changes in the oxidative stress, as indicated by 8OHdG and 8-isoprostane in the urine, and that of the antioxidant capacity, as determined by the PAO level in the serum. The levels of oxidative stress markers were increased after surgery, while the antioxidant capacity was decreased after surgery. The levels of 8OHdG in the urine were higher in the IeEN group on the thirteenth day after surgery, and the overall level was higher in the IeEN group. No differences were found in the 8-isoprostane in urine or in the PAO in serum between the groups at any point after surgery or overall. In short, no difference was observed in the levels of the oxidative stress marker, 8-isoprostane, or in the antioxidant capacity (based on the PAO) between the AeEN and IeEN groups, although the level of 8OHdG (another marker of oxidative stress) was found to have decreased to a greater extent by the AeEN.

As shown in Table 3, the mean and median length of SIRS after surgery were 1.8 ± 1.5 days and 1 day, respectively, in the AeEN group, while these were 3.4 ± 3.5 days and 1 day, respectively, in the IeEN group. No significant difference was found in the length of SIRS



	7 PreOD	1 PreOD	7 PostOD	13 PostOD
AeEN	6.71±0.44	6.91±0.44	5.99±0.22	6.50±0.46
IeEN	6.21±0.56	6.58±0.61	6.13±0.50	6.22±0.57
P-value	**0.085**	**0.938**	**0.165**	**0.103**

	7 PreOD	1 PreOD	7 PostOD	13 PostOD
AeEN	3.77±0.25	3.89±0.20	3.06±0.32	3.07±0.36
IeEN	3.50±0.47	3.75±0.54	3.04±0.49	2.96±0.57
P-value	**0.149**	**0.933**	**0.840**	**0.609**

	7 PreOD	1 PreOD	7 PostOD	13 PostOD
AeEN	223±38	242±44	147±36	184±46
IeEN	213±29	237±36	166±38	189±54
P-value	**0.393**	**0.409**	**0.053**	**0.072**

	7 PreOD	1 PreOD	7 PostOD	13 PostOD
AeEN	4.3±0.9	4.8±0.7	2.8±1.1	4.0±1.7
IeEN	3.5±1.2	4.3±1.2	2.9±1.1	3.8±1.8
P-value	**0.480**	**0.746**	**0.193**	**0.356**

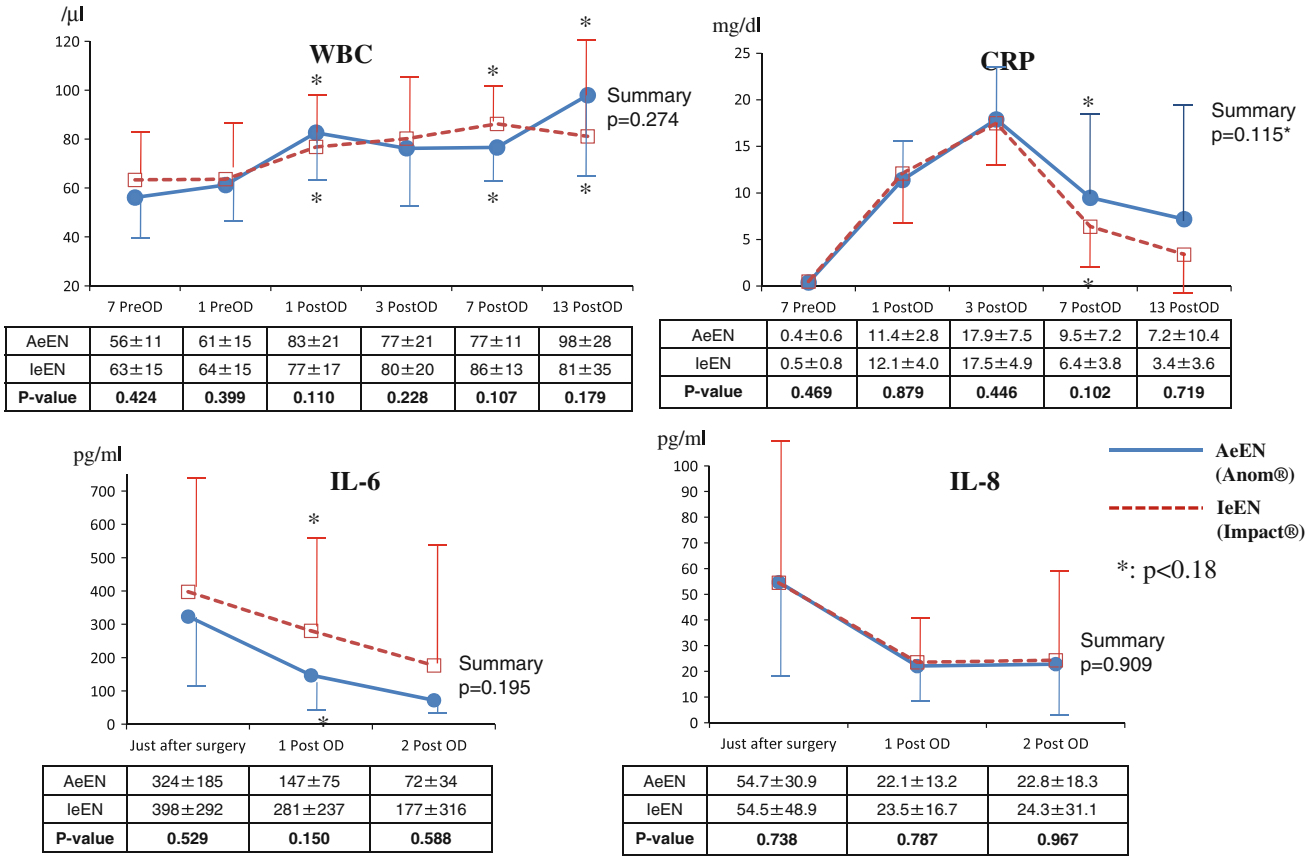
Fig. 3 The perioperative changes in nutritional markers

between the groups. The mean and median length of hospital stay after surgery were 39.6 ± 15.0 days and 35 days, respectively, in the AeEN group, and were 41.2 ± 12.0 days and 38 days, respectively, in the IeEN group. These values were not significantly different between the groups. Postoperative complications were observed in four (40 %) among the 10 patients in the AeEN group; anastomotic leaks developed in three patients (30 %) and surgical site infections (SSI) developed in three patients (30 %). Four (40 %) of the 10 patients in the IeEN group also developed postoperative complications; anastomotic leaks in developed in three (30 %), a SSI developed in one (10 %) and a pulmonary complication occurred in one (10 %) patient. No differences were observed in the incidences of postoperative complications between the groups.

Discussion

It is commonly considered that the preoperative use of IeNs including arginine, glutamine, omega-3-polyunsaturated fatty acids, nucleotides and other factors increases the immune response, decreases the postoperative complications and improves the patient outcomes after elective gastrointestinal surgery [1–4]. According to the consensus recommendations of the ASPEN, the preoperative use of IeNs at a dose of 1,200–1,500 ml/day for 5–7 days offers a benefit for patients undergoing an elective gastrointestinal surgery such as esophagectomy [6]. At the end of the recommendations, a list of the immune-enhancing formulas is provided. In the ESPEN guidelines on enteral nutrition, the perioperative management is focused on the ERAS. In those guidelines, the preoperative use of IeNs for 5–7 days is recommended for cancer patients undergoing major upper abdominal surgery [7].

The Impact® formula includes arginine, omega-3-polyunsaturated fatty acids and nucleotides, and it is specialized as an immune-enhancing diet. There were two trials comparing Impact® with the conventional enteral nutrients contained in Osmolite®. In critically ill patients in the ICU, the use of Impact® increased the immune response, however, it did not shorten the length of hospital stay [14]. In postoperative gastrointestinal cancer patients, the use of Impact® improved the immune function, and reduced the incidence of infections and wound complications by 70 % and shortened the length of hospitalization by 22 % [15].



	7 PreOD	1 PreOD	1 PostOD	3 PostOD	7 PostOD	13 PostOD
AeEN	56±11	61±15	83±21	77±21	77±11	98±28
IeEN	63±15	64±15	77±17	80±20	86±13	81±35
P-value	**0.424**	**0.399**	**0.110**	**0.228**	**0.107**	**0.179**

	7 PreOD	1 PostOD	3 PostOD	7 PostOD	13 PostOD
AeEN	0.4±0.6	11.4±2.8	17.9±7.5	9.5±7.2	7.2±10.4
IeEN	0.5±0.8	12.1±4.0	17.5±4.9	6.4±3.8	3.4±3.6
P-value	**0.469**	**0.879**	**0.446**	**0.102**	**0.719**

	Just after surgery	1 Post OD	2 Post OD
AeEN	324±185	147±75	72±34
IeEN	398±292	281±237	177±316
P-value	**0.529**	**0.150**	**0.588**

	Just after surgery	1 Post OD	2 Post OD
AeEN	54.7±30.9	22.1±13.2	22.8±18.3
IeEN	54.5±48.9	23.5±16.7	24.3±31.1
P-value	**0.738**	**0.787**	**0.967**

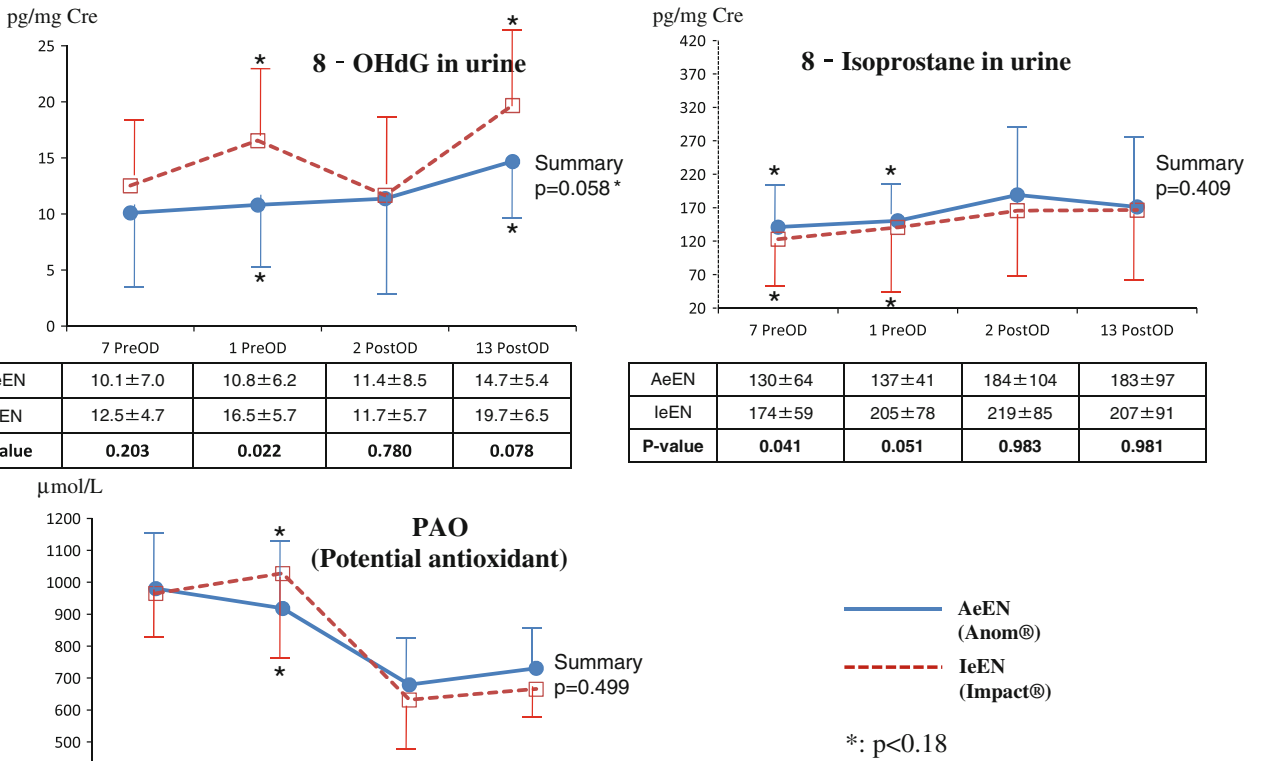
Fig. 4 The perioperative changes in inflammatory markers

However, despite the many promising findings, there are also negative data concerning the IeNs. A meta-analysis indicated that the arginine included in the IeNs is useful for patients undergoing elective surgery, but is harmful for septic patients [16]. In the Canadian Clinical Practice Guidelines, it is described that the arginine-containing enteral products should not be used for nutritional support for mechanically ventilated critically ill adult patients [17]. Moreover, it was reported that the IeNs do not offer a clinical benefit for adult ICU patients [18]. In the ESPEN Guidelines on Enteral Nutrition, the postoperative use of IeNs after uncomplicated surgery was given a C with regard to the level of recommendation [7]. In short, the preoperative use of IeNs seems to be useful for patients undergoing elective gastrointestinal surgery, but there is no evidence of efficacy regarding the postoperative use of IeNs for patients undergoing gastrointestinal surgery or in critically ill ICU patients.

It is considered that the use of antioxidants reduces the oxidative stress caused by surgery, trauma and other conditions, and thereby decreases the subsequent organ damage. AeEN was reported to increase the immune response in patients undergoing major gastrointestinal surgery [9]. Anom®, an AeEN includes antioxidants such as catechin and proanthocyanidin, as well as arginine, omega-3-polyunsaturated fatty acids, and nucleotides. However, it does not include as much of these components as the Impact formula.

There are negative data concerning the use of AeEN. For example, it was reported that the AeEN including glutamine and an antioxidant solution did not improve the prognoses of burned and major trauma patients [10], and that, while an AeEN including antioxidants, and vitamins A, C, and E improved the blood levels of antioxidants, it did not improve the clinical outcomes of patients [11]. According to the Canadian Clinical Practice Guidelines for nutritional support, glutamine-enriched formula should be considered for patients with severe burns and trauma, while the use of antioxidants and probiotics has no evidence to support its recommendation [17]. In short, the use of AeEN seems to increase the circulating levels of the immune response markers in patients undergoing major gastrointestinal surgery and those with severe burns and trauma, but there is no evidence that it improves the clinical outcomes after such surgery, or has any impact on critically ill ICU patients.

There is controversy with regard to the method of administration and the dose of the nutrients. Some



	7 PreOD	1 PreOD	2 PostOD	13 PostOD
AeEN	10.1±7.0	10.8±6.2	11.4±8.5	14.7±5.4
IeEN	12.5±4.7	16.5±5.7	11.7±5.7	19.7±6.5
p-value	**0.203**	**0.022**	**0.780**	**0.078**

	7 PreOD	1 PreOD	2 PostOD	13 PostOD
AeEN	130±64	137±41	184±104	183±97
IeEN	174±59	205±78	219±85	207±91
P-value	**0.041**	**0.051**	**0.983**	**0.981**

	7 PreOD	1 PreOD	2 PostOD	13 PostOD
AeEN	980±154	918±177	679±135	731±117
IeEN	965±131	1028±223	632±120	666±82
P-value	**0.954**	**0.108**	**0.319**	**0.209**

Fig. 5 The perioperative changes in oxidative stress markers and the antioxidant capacity

investigators have recommended that the supplements should be used only preoperatively and immediately after surgery. In the present randomized control trial, both the AeEN (Anom®) and the IeEN (Impact®) were administered at doses of 750–800 ml/day for 5 days before surgery, and for 7 days after surgery according to the standard clinical pathway at our hospital. The administration according to the protocols was successfully completed in both groups.

This pilot study was designed as a small randomized trial to investigate the potential equivalence or advantages in terms of various clinical effects using two types of nutrients. We focused on the perioperative courses and surgical outcomes after esophagectomy for cancer. The number of cases was designed to be small to discover any potential statistical differences in nutritional markers, immunoinflammatory markers, oxidative stress markers and other markers, and in the clinical outcomes between the groups. Because we included only a small number of cases, the results from this trial could be carefully and accurately controlled. There is commonly an imbalance between two groups in studies involving a small number of patients, which can be attributed to the pre-study values. Therefore, we formulated the following regression model for our analyses:

$$y = \beta 0 + \beta 1\ (\text{the previous value}) + \beta 2\ (\text{group}) + \gamma\ (\text{the previous value})(\text{group})$$

The p values at several time points were summarized using statistics which were constructed by adding $\beta 2$ at those time points. The AIC method was adopted for the statistical analysis, in which the model better corresponding to the obtained data was selected. If the model indicated no differences, then those data were assumed to be equivalent. The equivalence of the two groups was concluded, if the p value was <0.18 and no equivalence was considered to be present, if the p value was >0.18, because the number of patients in each group was 10. The probability of a false-positive finding in this AIC method was estimated to be less than 40 %.

All 20 patients could take food perorally. However, such patients are generally in a poor nutritional state due to their

disease. Nutritional markers such as the total protein, transferrin and RBP levels were low before nutritional therapy (on the sixth day before surgery), and increased after nutritional therapy (as indicated the day before surgery). The efficacy in terms of improving these markers was similar between Anom® and Impact®. After surgery, all four nutritional markers were decreased, and then the levels of transferrin and RBP (rapid turn-over proteins) increased on the thirteenth day after surgery. Such postoperative changes in nutritional markers were similar between the both groups. Accordingly, both diets seem to have similar effects on the nutrition of patients who undergo esophagectomy.

Concerning the immunoinflammatory markers, no differences were observed in the changes in the WBC, IL-6 and IL-8 levels throughout the perioperative period between the groups. However, the CRP level was more rapidly reduced after surgery in the IeEN group than in the AeEN group. With regard to the immunoinflammatory response, the IeEN (Impact®) seemed to be similar or slightly superior to the AeEN (Anom®) formula. Concerning the oxidative stress markers and the anti-oxidant capacity, no significant differences were observed in the changes in 8-isoprotane and PAO throughout the perioperative period. However, the level of 8OHdG was suppressed throughout the perioperative course in the AeEN group compared to the IeEN group. Therefore, with regard to the anti-oxidant capacity, the AeEN (Anom®) seems to be similar or slightly superior to the IeEN (Impact®).

One patient in the IeEN group developed aspiration pneumonia on the second day after surgery, when he underwent mini-cricothyroidotomy. In this patient, the level of IL-6 decreased from 794 pg/ml immediately after surgery to 388 pg/ml on the first day after surgery, when a tracheal tube was removed, and increased to 1,070 pg/ml on the second day after surgery when he was suffering from aspiration pneumonia. The SIRS period continued for 11 days after surgery. If this patient was excluded from the trial, the inflammatory markers were more equivalent between the groups. However, all 20 cases were enrolled based on randomization and all were analyzed according to the intent-to-treat.

The Impact® formula is an immune-enhancing diet including arginine, omega-3-polyunsaturated fatty acids and nucleotides. Omega-3-polyunsaturated fatty acids are considered to suppress the inflammation by competing against omega-6-polyunsaturated fatty acids to inhibit the production of prostaglandin E2 (PGE2) and leukotriene B4 (LTB4). It is also considered to suppress the inflammation by inhibiting NF-κB [19]. Arginine has many functions such as inhibiting bacterial growth, regulating T-cells and enhancing the production of the cytokines. It seems to suppress inflammation by means of NO [16]. Nucleotides, elements of DNA, are considered to enhance the movement of WBCs [20]. On the other hand, Anom® is antioxidant-enriched enteral nutritional supplement that include glutamine and polyphenol, while the content of arginine, omega-3-polyunsaturated fatty acids and nucleotides is lower than those present in the Impact® formula. Accordingly, both formulas seem to have strong points that differ from each other. However, no definitive difference was found in the postoperative changes in immunoinflammatory markers, oxidative stress markers or the antioxidant capacity between the diets. In addition, no large difference in the postoperative outcomes such as the duration of SIRS, the incidence of postoperative complications and the duration of hospital stay was found between the groups. This pilot trial therefore suggests that AeEN (Anom®) and IeEN (Impact®) showed a similar potential in terms of their perioperative effects for patients undergoing esophagectomy for cancer.

Conclusions

This pilot study suggested that the antioxidant-enriched enteral nutrition (Anom®) and the immune-enhancing enteral nutrition (Impact®) showed similar effects on nutrition, the immunoinflammatory reaction, the oxidative stress and on clinical outcomes after esophagectomy for cancer when used perioperatively. Further, large-scale studies are now warranted to determine whether these findings can be generalized to wider populations.

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Conflict of interest Takeshi Nagano has no conflict of interest to declare.

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