ANTICANCER RESEARCH *41*: 3875-3884 (2021)
doi:10.21873/anticanres.15182

OSK-0028 in Patients With Esophageal Cancer Undergoing Esophagectomy: A Double-blind, Randomised Controlled Trial

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Abstract. *Background/Aim: An excessive postoperative inflammatory response is correlated with the development of pneumonia and an unfavourable prognosis in patients undergoing esophagectomy for esophageal cancer. We assessed the influence of OSK-0028, a synthetic human ghrelin on inflammatory response and energy metabolism, on the postoperative course of patients following radical esophagectomy. Patients and Methods: Esophageal cancer patients were randomly assigned to low-dose (LD; 0.25 μg/kg/h) or high-dose (HD; 0.5 μg/kg/h) intravenous OSK-0028 or placebo for 7 days after esophagectomy. The primary endpoint was serum interleukin-6 level on postoperative day (POD) 3. Results: A total of 75 patients were enrolled (23 LD, 26 HD, 26 placebo). The median interleukin-6 levels on POD 3 were 40.95, 35.85, and 64.50 pg/ml in the placebo, LD, and HD groups, respectively, with no significant differences (p=0.78). Postoperative complications did not differ between groups. Bodyweight loss was significantly lower in patients receiving OSK-0028 than in those receiving placebo (–0.17% vs. 1.78%, p=0.043). Conclusion: Although OSK-0028 did not attenuate inflammatory response after esophagectomy, it prevented postoperative bodyweight loss.*

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Key Words: Esophageal cancer, inflammatory response, lean body mass, sarcopenia, synthetic ghrelin.

Although esophagectomy remains the mainstay of treatment for localised esophageal cancer, (1, 2) it is one of the most invasive gastrointestinal surgeries (3, 4). After esophagectomy, postoperative complications and excessive inflammatory responses such as systemic inflammatory response syndrome (SIRS) are associated with postoperative morbidity and mortality in patients with esophageal cancer (5).

OSK-0028 is an injectable, synthetic human ghrelin. Ghrelin is a peptide hormone secreted mainly in the stomach. In 1999, it was identified as an intrinsic ligand for the growth hormone (GH) secretagogue receptor of the pituitary gland (6). Ghrelin has several physiological functions in humans, including promoting GH secretion, enhancing appetite, and stimulating gastrointestinal activity (7-9). In addition, ghrelin has been reported to exert anti-inflammatory effects by reducing pro-inflammatory cytokine production *via* nuclear factor-kB inhibition (10, 11). Studies show that an early postoperative decrease in plasma ghrelin levels was correlated with prolonged SIRS after esophagectomy, (12) and supplementation of exogenous ghrelin showed suppression of postoperative peak of inflammatory cytokines in the small pilot study (13). These studies suggest that ghrelin may be useful to reduce postoperative inflammation and pulmonary complications after esophagectomy.

In view of these findings, we initiated this double-blind, randomised-controlled trial at three different Institutions to confirm the superiority of ghrelin administration compared to placebo in terms of suppressing postoperative inflammatory response. We performed this study in compliance with Good Clinical Practices under the rules of Japanese pharmaceutical jurisprudence to approve OSK-0028 as a new drug for postoperative inflammatory response.

Patients and Methods

Study design and participants. This double-blind, randomised-controlled trial was performed at three specialised hospitals to assess the effects of human ghrelin (UMIN Clinical Trials Registry: UMIN000026115). We set a three-armed trial to assess dose-related effect of OSK-0028. Eligible patients were those aged over 20 years with histologically proven thoracic esophageal cancer and an Eastern Cooperative Oncology Group performance status of 0 or 1. Exclusion criteria were tumor invasion of adjacent organs, active coexisting cancer, current dialysis, systemic administration of corticosteroids, participation in another drug trial, and pregnancy. All patients provided their written informed consent. The study protocols were approved by the institutional review board or independent Ethics Committee at each participating hospital, and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice Guidelines, and the Declaration of Helsinki.

Randomisation and masking. Patients were randomly assigned (1:1:1) to receive infusion of low-dose OSK-0028 (LD; 0.25 μg/kg/h), high-dose OSK-0028 (HD; 0.5 μg/kg/h), or placebo (saline solution) for 7 days during and after esophagectomy. For the randomisation, we used the permuted block method with stratification by institution. An independent statistician provided a computer-generated list of random set numbers in permuted blocks of six. The hospital pharmacist packed the study medications in identical blank tubes with a code number according to the randomisation list. The pharmacist kept the list of code numbers in a sealed envelope and was not involved in data analysis or outcome assessment. Research staff used these code numbers to provide eligible patients with the correct drug supply kits, and those assessing outcomes and analysing data were masked to the patients' assigned intervention groups throughout the study.

Perioperative procedure. Patients received intravenous LD or HD OSK-0028 or placebo from the start of surgery for 7 days though a central venous catheter; the dose was calculated based on bodyweight on the day before surgery. Patients could withdraw from the study at any time, or be withdrawn at the discretion of the investigator if there was a major protocol violation or if adverse events occurred that required study drug cessation. No dose reductions or interruptions were planned. Our surgical procedure consisted of subtotal esophagectomy with mediastinal lymphadenectomy *via* right thoracotomy or video-assisted thoracic surgery (VATS), upper abdominal lymphadenectomy, reconstruction with a gastric tube *via* the posterior mediastinum or retrosternally, and anastomosis *via* cervical incision. Cervical lymphadenectomy was performed in patients with upper thoracic esophageal cancer or with middle or lower thoracic esophageal cancer and supraclavicular or recurrent laryngeal nerve lymph node metastasis diagnosed by radiological imaging. Methylprednisolone (250 mg/body, only on the day of surgery) was administered intraoperatively to all patients right before the thoracotomy incision. Feeding tubes were placed in all cases and tube feeding was performed from postoperative day (POD) 1.

Data collection. Blood tests and X-ray imaging were performed every day from POD 1 to POD 7, and on PODs 10 and 14. Chest computed tomography (CT) was performed before surgery and on POD 7 to detect pulmonary complications. Bodyweight was measured at baseline (within 7 days before surgery), and at PODs 7 and 14 with a calibrated scale dedicated for use in this study. In patients who were treated at the Osaka University Hospital, body composition (lean body mass and fat mass) was measured with dual-energy X-ray absorptiometry (DXA) before surgery and at POD 10. Treatment-emergent adverse events that occurred within 2 weeks after surgery were graded by the site investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Outcomes. The primary endpoint was serum interleukin-6 level on POD 3. The secondary endpoints were pneumonia, disordered sputum expectoration, postoperative complications, the duration of SIRS, serum C-reactive protein (CRP) level, serum interleukin-6 level, changes of bodyweight and body composition, and adverse events. Screening for all complications and SIRS were performed daily on PODs 1 through 7. Postoperative complications were categorised according to the Clavien-Dindo classification system(14). SIRS was diagnosed when two or more of the following criteria were met: 1) body temperature under 36˚C or over 38˚C; 2) heart rate over 90 beats per minute; 3) tachypnea of more than 20 breaths per minute or an arterial partial pressure of carbon dioxide under 32 mm Hg; and 4) white blood cell count under 4,000 cells/mm3, over 12,000 cells/mm3, or a proportion of immature (band) forms greater than 10%. Changes of bodyweight and body composition were evaluated by calculating the percent reduction at each time point relative to baseline.

Statistical analysis. Efficacy and safety analyses were performed on the full analysis set (FAS) consisting of all patients who received OSK-0028 after randomisation. Sensitivity analysis was performed on the per-protocol set (PPS). Continuous variables are represented as median and range or mean and SD, and categorical variables are represented as frequencies and proportions. Perioperative changes in interleukin-6 and CRP levels are shown in a box-whisker plot. For comparison between groups at 3 days after esophagectomy, Williams' test was performed with the logarithmic transformation to approximate the normal distribution, assuming a dose-response relationship. The SIRS resolution rate in each group was estimated by the Kaplan–Meier method, and the log-rank test was used for comparison between groups. The rates of postoperative bodyweight loss, lean body mass loss, and amount of fat loss were compared between the two groups with and without OSK-0028 using the *t*-test. Statistical tests were two-sided and significance was defined as $p<0.05$. All analyses were performed using SAS ver.9.4 (SAS Institute Inc., Cary, NC, USA).

Sample size. Based on the results of our previous study, the mean and standard deviation of logarithmic transformations of the serum interleukin-6 level on POD 3 were 3.50±0.91 and 4.58±1.09, respectively, in the HD and placebo group. It was assumed that the LD group showed half the effect of the HD group. In order to detect at least a significant difference between the HD group and the placebo group, the sample size that achieved a significance level of 2.5% on one side and a power of 80% was 15 patients per group. In addition, the incidence of pulmonary complications in the previous study was 10% in the HD group and 45% in the placebo group. To detect this difference by the Chi-square test with a significance level of 5% on both sides and a power of 80%, at least 25 patients per group were required. Therefore, the required sample

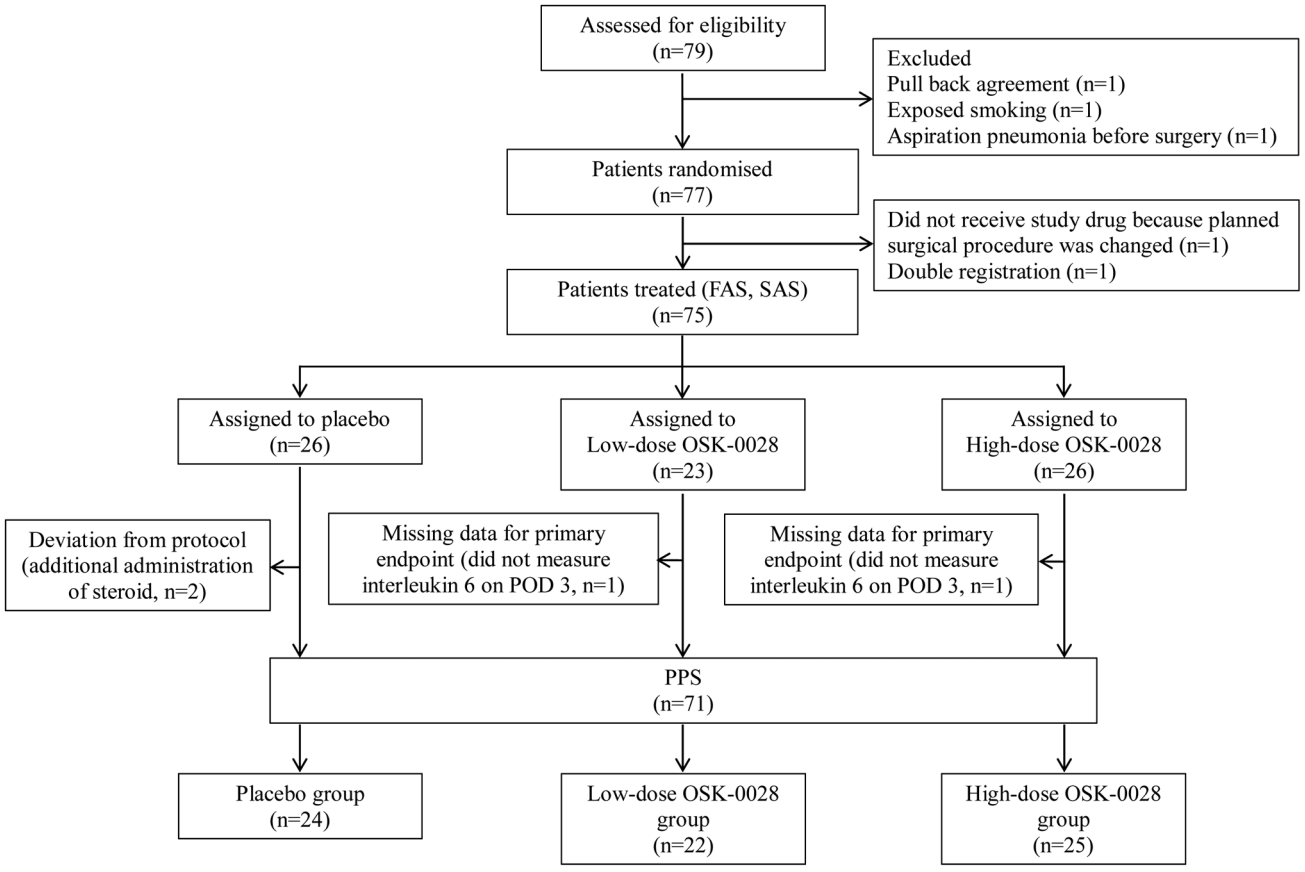


Figure 1. *Trial profile. FAS indicates full analysis set. PPS, Per protocol set.*

size was determined to be 25 patients per group, for a total of 75 patients. In consideration of dropout, the target sample size was set to 80 patients.

Results

Patients. The study flow diagram is summarised in Figure 1. From February, 2017, to August, 2018, 75 patients were enrolled in the study. In total, 75 patients were included in the FAS. The enrolled patients were randomised into the low- or high-dose OSK-0028 groups or the placebo group, with 71 patients included in the PPS. Patient background data are shown in Table I. In brief, there were 65 (86.7%) males and 10 (13.3%) females, with a median age of 68.0 years (range=41-83 years). All patients underwent esophagectomy for thoracic esophageal cancer. Factors that might influence postoperative inflammatory response, including surgical procedure, operation time, and intraoperative blood loss, did not differ between groups. Clinical stage III or IV patients were more in HD group (53.9%) than those in Placebo group (26.9%) or those in LD group (34.7%), then clinical stage of esophageal cancer was statistically different between the groups (p=0.033).

Administration of OSK-0028 and adverse events. The trend of ghrelin blood levels during OSK-0028 administration in patients who underwent esophagectomy at the Osaka University Hospital is shown in Figure 2. Ghrelin concentration rose rapidly in patients who received OSK-0028, and reached a higher peak in the HD group than in the LD group. High ghrelin blood levels continued during OSK-0028 administration and decreased quickly afterwards. Adverse events which could not be proven to have no causal connection to OSK-0028 occurred in two patients, one with hyperhidrosis and another with itching. There were no critical adverse events.

Trend of inflammatory response after esophagectomy. The serum interleukin-6 levels in each group increased on POD 1 and gradually decreased from POD 3 to POD 7 (Figure 3a). In the FAS, the median interleukin-6 level on POD 3 was 40.95 (2.31-299.00) pg/ml in the placebo group, 35.85

Table I. *Patient characteristics*.

	Placebo n=26 (%)	Low-dose OSK-0028 n=23 (%)	High-dose OSK-0028 n=26 (%)	*p*-Value
Age; years, median, range	68.5, 53-83	68.0, 47-82	68.0, 41-80	0.93
Gender				0.56
Male	24 (92.3)	19 (82.6)	22 (84.6)	
Female	2 (7.7)	4 (17.4)	4 (15.4)	
cStage				0.033
I	9 (34.6)	11 (47.8)	9 (34.6)	
II	10 (38.5)	4 (17.4)	3 (11.5)	
III	5 (19.2)	3 (13.0)	12 (46.2)	
IV	2 (7.7)	5 (21.7)	2 (7.7)	
Preoperative treatment				0.41
Non	9 (34.6)	10 (43.5)	6 (23.1)	
DCF	17 (65.4)	13 (56.5)	19 (73.1)	
DCF-RT	0	0	1 (3.8)	
Surgical procedure				0.51
VATS	15 (57.7)	15 (65.2)	19 (73.1)	
Open thoracotomy	11 (42.3)	8 (34.8)	7 (26.9)	
Operation time; minutes, median, range	526, 338-728	483, 409-794	525.5, 371-828	0.44
Blood loss; ml, median, range	255, 40-810	195, 60-626	255, 30-1105	0.53

Percentage is calculated using the number of patients in the column heading as the denominator. DCF, Docetaxel, cisplatin, and 5-fluorouracil; DCF-RT, docetaxel, cisplatin, and 5-fluorouracil combined with radiotherapy; VATS, video-assisted thoracic surgery.

(4.84-193.00) pg/ml in the LD group, and 64.50 (14.80-242.00) pg/ml in the HD group, with no significant differences (p=0.78). In the PPS, the median interleukin-6 level on POD 3 was 42.15 (6.74-299.00) pg/ml in the placebo group, 35.85 (4.84-193.00) pg/ml in the LD group, and 64.5 (14.80-242.00) pg/ml in the HD group, again with no significant differences (p=0.62). The median interleukin-6 levels were also similar between the groups on PODs 1, 5, and 7. The serum level of IL-6 on POD 3 tended to be higher in males, patients with longer operation time, patients with more blood loss, and patients with higher preoperative serum CRP, and was significantly correlated with the occurrence of postoperative complications including pneumonia. (Table II). The highest serum CRP level was measured on POD 3 in all three groups (Figure 3b). The median CRP levels were similar between the groups on PODs 1, 2, 3, 4, 5, 6, 7, 10, and 14. The SIRS duration in each group is shown in Figure 4; there were no significant differences between the groups (p=0.49). The percentages of patients in whom SIRS had resolved by POD 7 were 61.5% in the placebo group, 64.5% in the LD group, and 69.2% in the HD group.

Postoperative complications. The occurrence of postoperative complications is summarised in Table III. The incidence of postoperative pneumonia and atelectasis was numerically lower in the LD group than in the other two groups, but there were no significant differences (p=0.68, p=0.76). Anastomotic leakage occurred with greater frequency in the HD group than in the other groups, but again the differences were not significant (p=0.53).

Postoperative body composition. Bodyweight loss on POD 7 was significantly higher in the placebo group than in patients who received OSK-0028 (median, ghrelin *vs*. placebo group, 0.00% *vs*. 2.18%, p=0.043, Figure 5a). However, the difference on POD 14 was not statistically significant. Although fat loss on POD 10 in patients who were treated at the Osaka University Hospital was similar between the placebo and OSK-0028 groups (Figure 5c, p=0.51), the lean body mass loss was higher in the placebo group than in the OSK-0028 groups (median, ghrelin *vs*. placebo group, 3.89% *vs*. 3.94%, p=0.086, Figure 5b).

Discussion

We evaluated the anti-inflammatory effects of OSK-0028 after esophagectomy in this investigator-initiated, randomised control trial. Although administration of OSK-0028 to esophageal cancer patients who underwent esophagectomy was safe, no anti-inflammatory effects were observed in this setting. Postoperative serum interleukin-6 and CRP levels, as well as postoperative complications such as pneumonia, were unaffected by OSK-0028 administration. In terms of drugs to suppress postoperative inflammation, it was reported that

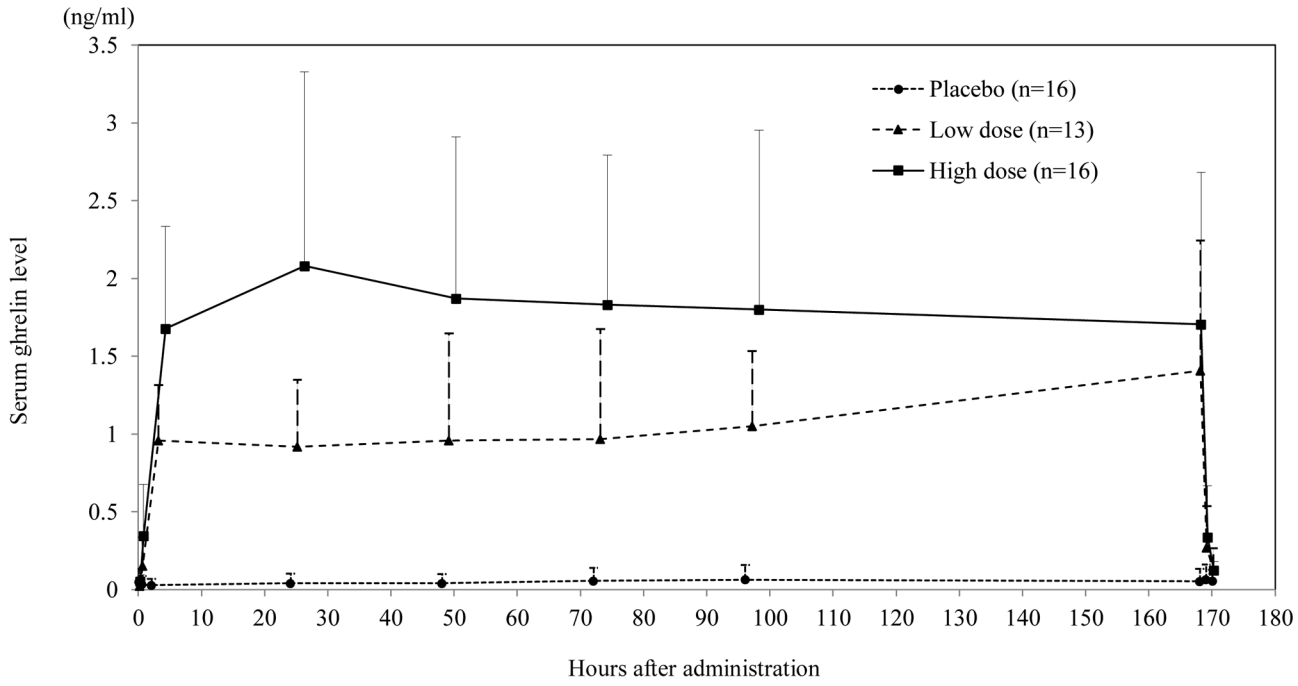


Figure 2. *Perioperative changes of blood ghrelin levels in patients treated at the Osaka University Hospital. Ghrelin levels were measured preoperatively, 30 min and 2 h after the initiation of surgery, and on postoperative days 1, 2, 3, 4, and 7.*

Table II. *Relationship between serum IL-6 level on POD 3 and clinical factors.*

	Low serum IL-6 on POD 3 n=38 (%)	High serum IL-6 on POD 3 n=37 (%)	*p*-Value
Age; years, median, range	68.5, 41-82	68, 53-83	0.93
Gender			
Male	30 (78.9)	35 (94.6)	0.086
Female	8 (21.1)	2 (5.4)	
Body mass index, kg/m^2, median, range	23.1, 16.8-29.6	21.8, 16.5-27.1	0.48
cStage			
I, II	25 (65.8)	21 (56.8)	0.48
III, IV	13 (34.2)	16 (43.2)	
Surgical procedure			
Open thoracotomy	11 (28.9)	15 (40.5)	0.34
VATS	27 (71.1)	22 (59.5)	
Field of lymphadenectomy			
2-Fields	18 (47.4)	18 (48.6)	1.00
3-Fields	20 (52.6)	19 (51.4)	
Operation time; minutes, median, range	512, 371-728	535, 338-828	0.085
Blood loss; ml, median, range	170, 30-810	240, 50-1105	0.073
Preoperative serum IL-6	1.84, 0.64-19.8	2.09, 0.86-18.6	0.18
Preoperative serum CRP	0.06, 0.01-1.48	0.09, 0.02-2.48	0.061
Postoperative complications (C-D classification)			
Grade 0-2	28 (73.7)	15 (40.5)	0.005
Grade 3 or higher	10 (26.3)	22 (59.5)	
Postoperative pneumonia	1 (2.6)	9 (24.3)	0.007

VATS, Video-assisted thoracic surgery; IL-6, interleukin-6; CRP, C-reactive protein; C-D, Clavien-Dindo; POD, postoperative day.

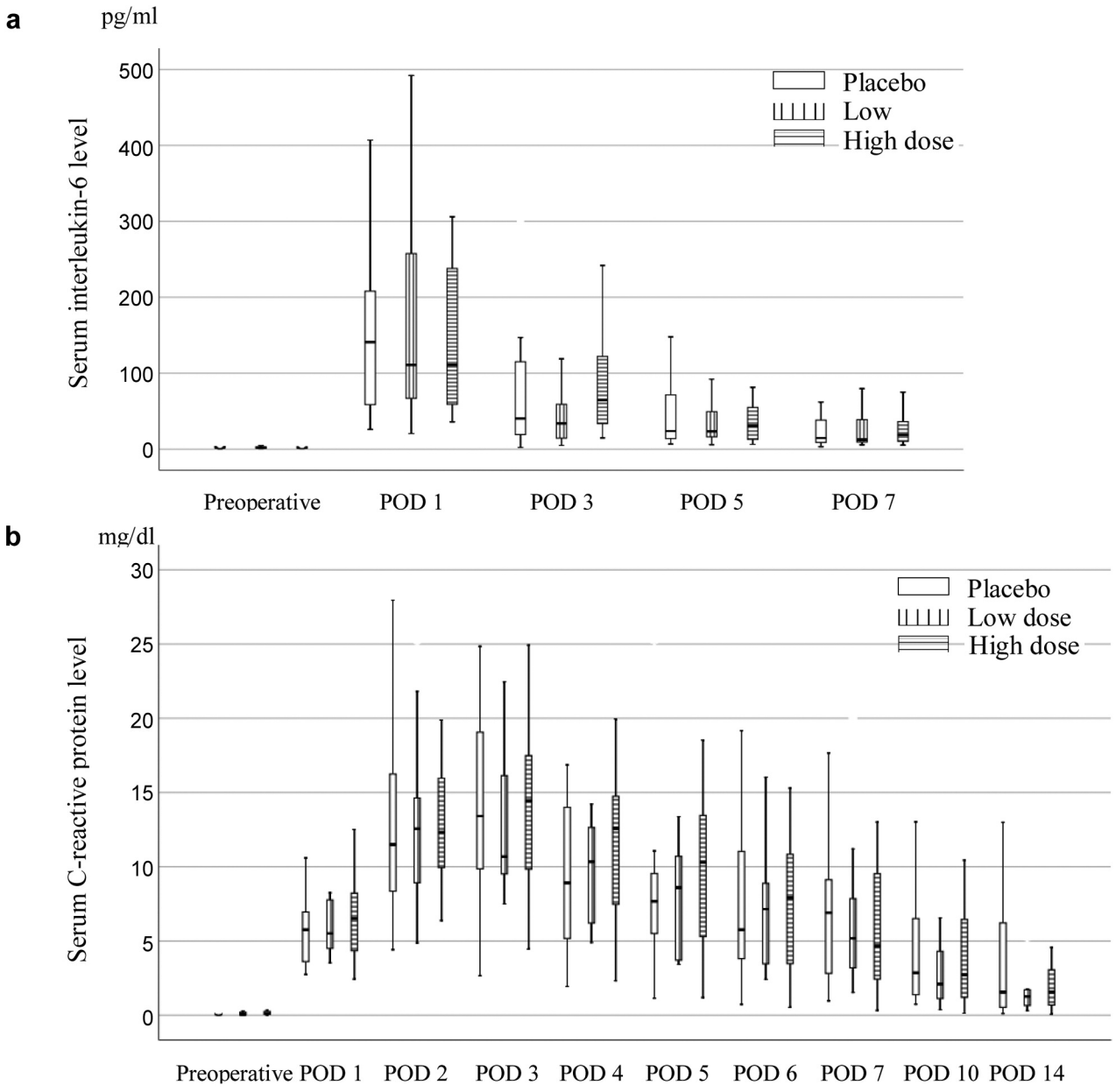
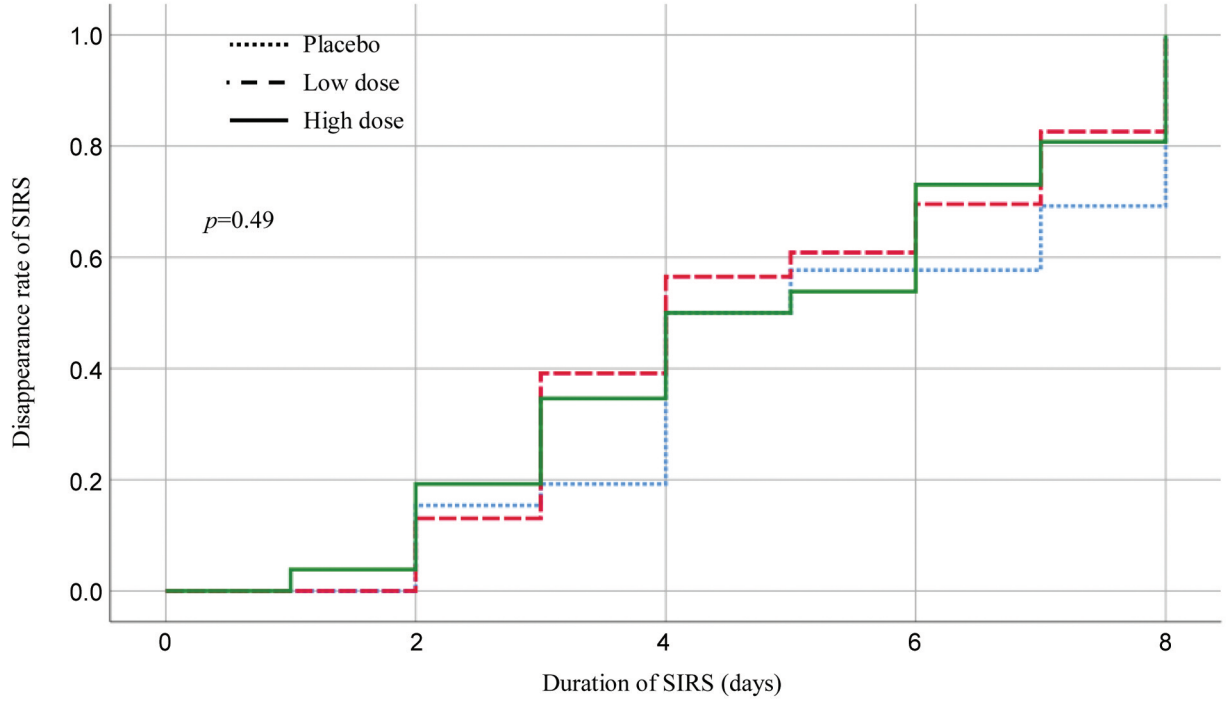


Figure 3. *Perioperative changes in serum levels of interleukin-6 (a) and C-reactive protein (b). Interleukin-6 levels were measured preoperatively and on postoperative days 1, 3, 5, and 7. CRP levels were measured preoperatively and on postoperative days 1, 2, 3, 4, 5, 6, 7, 10, and 14.*

Table III. *Postoperative complications (Clavien-Dindo classification ≥II).*

	Placebo n=26 (%) n=23 (%)	Low-dose OSK-0028 n=26 (%)	High-dose OSK-0028	*p*-Value
Pneumonia	4 (15.4)	1 (4.3)	5 (19.2)	0.68
Atelectasis	9 (34.6)	4 (17.4)	10 (38.5)	0.76
Anastomotic leakage	3 (11.5)	2 (8.7)	5 (19.2)	0.53
All complications	21 (80.8)	13 (56.5)	19 (73.1)	0.17



Number at risk									
Placebo	26	26	26	22	21	13	11	11	8
Low dose	23	23	23	20	14	10	9	7	4
High dose	26	26	25	21	17	13	12	7	5

Figure 4. *Systemic inflammatory response syndrome (SIRS) duration after esophagectomy in the placebo and low- and high-dose OSK-0028 groups.*

perioperative corticosteroid administration prevented postoperative complications after esophagectomy, (15) and the 2017 esophageal cancer practice guidelines edited by the Japan Esophageal Society recommend perioperative administration of methylprednisolone (16). Our study shows that OSK-0028 cannot augment the effects of corticosteroids. On the other hand, OSK-0028 reduced postoperative body weight loss.

Ghrelin has been reported to suppress excessive inflammatory responses by inhibiting pro-inflammatory cytokine production, mononuclear cell binding, and nuclear factor-kB activation (10, 11). Unexpectedly, however, the present study did not show any anti-inflammatory effect of ghrelin. On the other hand, the serum IL-6 on POD 3 was shown to be a surrogate marker for pneumonia. One possibility of those unexpected results was the difference of clinical stage of esophageal cancer between groups. Esophageal cancer patients with advanced clinical stage, which might require more invasive esophagectomy and cause higher postoperative inflammatory response, was more in HD OSK-0028 group than LD OSK-0028 group or Placebo group. Prior to the start of this study, we did not believe that the degree of progression would affect the results, so it was not added to the randomization allocation factors. In short, we considered that the inflammatory response after esophagectomy in esophageal cancer patients might not be an appropriate subject of study because it is influenced by significant surgical stress, postoperative complications, and progression of disease.

A new finding in the present study was that continuous administration of OSK-0028 was associated with preserved body weight after esophagectomy. Previous studies reported an orexigenic or anabolic effect of human ghrelin (7, 8). We also performed several clinical randomised trials using synthetic ghrelin, targeting appetite and bodyweight loss after chemotherapy or surgery for upper gastrointestinal cancer (17-19) but none of the previous studies, including our own, used continuous infusion. For the first time, the current study demonstrated an anabolic effect of continuous synthetic ghrelin administration to esophageal cancer patients who underwent esophagectomy. However, the anti-catabolic effect of OSK-0028 continued only during drug

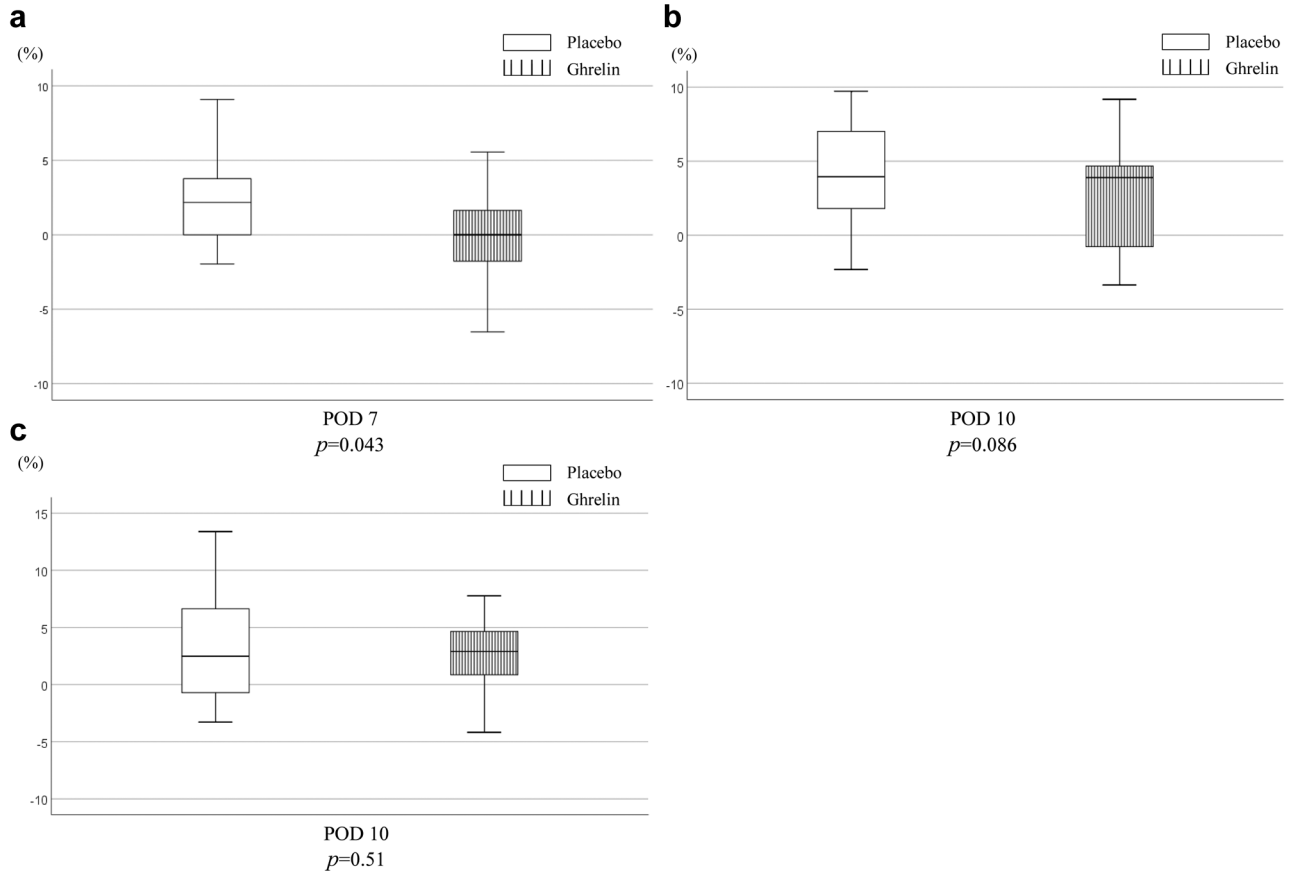


Figure 5. *Rate of bodyweight loss on POD 7 in all patients (placebo group n=25, OSK-0028 group n=47). (a) Body composition was measured in 44 patients on POD 10 (placebo group n=16, OSK-0028 group n=28). The rate of lean body mass loss (b) and fat loss (c) were compared between groups.*

administration and diminished a few days after it was discontinued. Another important point was that the total caloric intake was equal between three groups in present study. A previous study reported that ghrelin administration increased oral caloric intake and sustained bodyweight in patients who underwent surgery (17, 18), so total caloric intake increased in patients who received ghrelin. This result implied that ghrelin administration could directly modulate body composition, especially muscle metabolism. Some studies showed that ghrelin facilitated muscle regeneration and prevented muscle atrophy regardless of its orexigenic effect (20, 21). The present study is the first to verify ghrelin's effect on metabolism in patients with esophageal cancer.

This study had several limitations. First, although this was randomised, controlled trial performed at multiple Centers, the number of patients in each group was relatively small. Although we assumed it would be possible to demonstrate the anti-inflammatory effect of OSK-0028 in this setting based on the data of our previous study, it turned out that the number of patients was insufficient to prove our hypothesis. The reasons for this was that the incidence of anastomotic leakage was higher compared to our expectations, while that of postoperative pneumonia was lower. Second, it may not be ideal to evaluate the postoperative inflammatory response in patients undergoing esophagectomy because inflammation after esophagectomy is adversely affected by numerous factors, including surgical stress, postoperative complications, and disease progression. Third, it has been reported that ghrelin expression in tumors correlates with tumor progression (22), and the possibility that ghrelin administration may promote tumor growth cannot be completely ruled out. This possibility needs to be verified in future prognostic analyses.

In conclusion, OSK-0028 was safely administered to esophageal cancer patients who underwent esophagectomy. Although OSK-0028 could not attenuate the inflammatory response after esophagectomy, it did prevent postoperative bodyweight loss. We believe that these findings will contribute to improvements in perioperative management for patients with esophageal cancer.

Conflicts of Interest

All Authors have no conflicts of interest or financial ties to disclose.

Authors' Contributions

Study Desig: Kotaro Yamashita, Yasuhiro Miyazaki, Daisaku Nakatani, Hiroyuki Araki, Tomomi Yamada, Yuichiro Doki; Implementation of trial treatment: Yasunori Masuike, Koji Tanaka, Keijiro Sugimura, Tomoki Makino, Osamu Shiraishi, Tsuyoshi Takahashi, Yukinori Kurokawa, Makoto Yamasaki, Hiroshi Miyata, Yutaka Kimura, Takushi Yasuda, Masahiko Yano, Hidetoshi Eguchi; Collecting the data: Kotaro Yamashita, Yasuhiro Miyazaki; Analyzing, and interpreting the data: Kotaro Yamashita, Yasuhiro Miyazaki, Hiroyuki Araki, Tomomi Yamada; Writing the report: Kotaro Yamashita, Yasuhiro Miyazaki; Making the decision to submit for publication: Kotaro Yamashita, Yasuhiro Miyazaki, Takushi Yasuda, Masahiko Yano, Yuichiro Doki.

Acknowledgements

The trial was supported by the Department of Medical Innovation at Osaka University Hospital. The Authors would like to thank the patients and investigators for their participation in this study. Secretarial operation and clinical research coordination were provided by Ms. Chiaki Okamoto. Medical writing and editorial assistance were provided by Dr. Manabu Yamaji, PhD, and Ms. Mayuko Ouchi. Data collection and patient support were provided by Ms. Namie Taichi, and Ms. Kaori Osakada. The authors are responsible for all content and editorial decisions. This research was supported by Japan Agency for Medical Research and Development under Grant Number JP17lk1403001.

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Received May 31, 2021
Revised June 12, 2021
Accepted June 22, 2021