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Original Article

Changes of plasma gastrointestinal peptides after otolaryngological surgery: A prospective observation study in patients with head and neck disorders

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ABSTRACT

Gastrointestinal (GI) problems in critically ill patients are common and are associated with impaired outcomes, and GI tract dysfunction can become a prognostic factor after surgery. Clinical studies have demonstrated that plasma concentrations of different biomarkers, such as motilin and ghrelin, may reflect various aspects of GI function. The aim of this study is to evaluate the relationship between GI motility and the plasma concentrations of three GI peptides (motilin, acyl-ghrelin, and desacyl-ghrelin) after otolaryngological surgery. In this prospective single-center observational study, the records of 11 patients were analyzed. The GI response was assessed by the observation of defecation, bowel sounds, or bowel distension within five days after otorhinolaryngological surgery. Differences between the GI response and nonresponse groups were analyzed through changes in the GI peptides. A significant difference in motilin changes was observed between the GI response and nonresponse patient groups, suggesting that the plasma concentration of motilin is correlated with gastrointestinal motility after otolaryngological surgery. These results might suggest that motilin could be an index reflecting GI motility after otorhinolaryngological surgery.

KEYWORDS: gastrointestinal peptide, gastrointestinal motility, motilin, ghrelin.

1. INTRODUCTION

Gastrointestinal (GI) problems in critically ill patients are common and are associated with impaired outcomes; hence, GI tract dysfunction can become a prognostic factor after surgery [1-3]. Approximately 50-80% of all critically ill patients will develop at least one GI symptom after surgery. Such GI symptoms can be predictors of mortality. For example, during the first week after surgery, GI dysfunction occurred and was associated with higher 28-day mortality [2]. Symptoms include abdominal pain, feeding intolerance, constipation and diarrhea. GI dysfunction, especially the loss of GI motility, is undesirable, making the management of GI motility after surgery important. At present, the lack of markers for the measurement of GI function has suppressed studies in this field, as well as the assessment of GI dysfunction as an organ failure. Although plasma citrulline and intestinal fatty acid binding proteins have been proposed as possible markers for GI function [4], their clinical use in the diagnosis and management

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of GI hypofunction is still unclear. GI hypofunction in critically ill patients is probably underestimated and associated with a poor prognosis; however, a validated definition of GI hypofunction remains elusive in the absence of a marker to measure it [5].

Experimental and clinical studies have demonstrated that plasma concentrations of different biomarkers, such as GI peptides, may well reflect various aspects of GI function. Physiological functions such as GI motility and appetite are controlled under coordination of the neuroendocrine-immune system. In recent years, several GI peptides, such as motilin and ghrelin, have been subjects of interest for researchers. It is well known that changes in the plasma concentrations of GI peptides are related to the degree of GI function [6]. Changes in the release of GI peptides also provide information about pathological conditions because they are under the control of various nervous systems. Ghrelin is a peptide composed of 28 amino acid residues and has a characteristic structure in which serine 3 residue is modified (acylated) by n-octanoic acid, a fatty acid having 8 carbon atoms, as the first endogenous ligand for the growth hormone secretagogue receptor (GHSR) isolated from the stomach [7].

There are two types of ghrelin, acyl-ghrelin and desacyl-ghrelin, owing to differences in their side chains. Acyl-ghrelin was thought to be an active type, and has been also reported in recent years to have various physiological effects [7]. Acyl-ghrelin is a peptide mainly produced by gastric endocrine cells and having important effects on energy metabolism control, such as food intake increase, weight gain, and control of GI tract function [8]. The other GI peptide mentioned above, motilin, accelerates gastric emptying, especially during the interdigestive state. Plasma motilin is coupled with strong peristaltic contractions; these migrating waves are known as the phase III contractions of interdigestive migrating contractions [9, 10]. At present, it is unclear whether there is any change in the plasma concentrations of GI peptide after otorhinolaryngological surgery.

The aim of this study is to evaluate the relationship between GI function (GI motility) and the plasma concentrations of three GI peptides (acyl-ghrelin, desacyl-ghrelin, and motilin) after otorhinolaryngological surgery in patients with head and neck disorders.

2 MATERIALS AND METHODS

2.1. Patient eligibility

Eleven patients expected to require intensive care for at least three days between February 1, 2018, and December 31, 2019, were enrolled in the intensive care unit, Oita University Hospital. Clinically ill patients who underwent insertion into the nasal canal and analgosedation and who agreed to this study themselves or through legally authorized representatives were included. The exclusion criterion was an age < 20 years. All patients were supplied nourishment *via* enteral feeding (liquid) and not by oral intake within 24-48 hr after otolaryngological surgery. Any medicines that might possibly have affected GI motility and functions, including prokinetic drugs, were prohibited for 5 days during the study.

2.2. Assessment of gastrointestinal motility

The evaluation of GI motility was carried out by the confirmation of the presence or absence of defecation, bowel sounds, and bowel distension by the medical practitioner at days 0, 1, 3, and 5 after otolaryngological surgery. The GI response group was defined as patients presenting these signs (defecation, bowel sounds, or bowel distension) without treatment of prokinetic drugs. The GI nonresponse group was defined as patients who did not present the signs [11].

2.3. Blood sampling

Blood samples were collected into chilled tubes containing ethylenediaminetetraacetic acid at 7 a.m. after an overnight fast on days 0, 1, 3, and 5 after otolaryngological surgery in Oita University Hospital. The samples were immediately transferred into chilled tubes, which were centrifuged at approximately 2,500 rpm for 20 min at 4 ºC. The plasma was then transferred to a polypropylene tube and stored frozen at -80 ºC. The plasma samples for all the peptide measurements were mixed with aprotinin (500 KIU/mL) and for acyl-ghrelin and desacyl-ghrelin with 0.1 N hydrochloric acid. The plasma GI peptide (acyl-ghrelin, desacyl-ghrelin, and motilin) concentrations

were measured by enzyme immunoassay. The fluorescence intensity was measured using a microplate reader.

2.4. Data analysis and statistics

Continuous variables are expressed as mean ± standard deviation (SD) (range). The data showed a percentage for the plasma concentration of GI peptides on day 0. An independent analysis of variance and a Bonferroni test were performed to compare the motilin, acyl-ghrelin, and desacyl-ghrelin patterns. Statistical differences were analyzed by a Mann-Whitney U-test between the GI response and nonresponse groups. P values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SPSS software package (version 20.0; SPSS Inc., IL, U.S.A.).

2.5. Ethics

This study was performed in accordance with the Declaration of Helsinki and its amendments. The protocol was approved by the Oita University medical department's and Fukuyama University's ethical review boards (approval numbers: 1369 and R1-29, respectively). Each patient received information about the scientific aim of this study and provided written informed consent.

3. RESULTS

3.1. Patient characteristics

In total, 11 patients aged 66.0 ± 14.3 years (range 44 to 89) were reviewed. Table 1 shows the characteristics of the 11 patients on the first day (day 0) after otorhinolaryngological surgery. Of the 11 patients, 5 were assessed as showing a GI response (Nos. 1-5) and 6 as showing a GI nonresponse (Nos. 6-11) (Table 1).

3.2. Evaluation of plasma gastrointestinal peptide concentrations

The time profile of plasma GI peptide concentrations after otorhinolaryngological surgery in patients (days 0, 1, 3, 5) is shown in Figure 1. The plasma motilin concentrations on day 5 were significantly higher than those on day 0 (P = 0.0413, 143.8 ± 47.4% at day 5) (Figure 1a). Similarly, the plasma acyl-ghrelin concentrations on day 1 were significantly higher than those on day 0 (P = 0.0025, 173.8 ± 53.5% at day 1). However, the plasma acyl-ghrelin concentrations on days 3 and 5 were

Table 1. Patient characteristics.

No.	Age (years)	Gender	BMI (kg/m^2)	Diagnosis	Defecation and gastrointestinal movements
1	71	M	20.3	Radioactive necrosis of the jaw bone	+
2	86	F	21.5	Maxilla tumor	+
3	61	M	21.0	Bladder cancer	+
4	53	M	25.7	Oral cancer	+
5	70	M	25.5	Postoperative facial paralysis	+
6	79	M	17.3	Tongue cancer	-
7	44	M	34.0	Tongue cancer	-
8	54	M	30.5	Fournier gangrene	-
9	63	M	24.3	Buccal mucosa tumor	-
10	57	F	15.3	Tongue cancer	-
11	89	F	17.7	Tongue cancer	-

BMI; Body mass index.

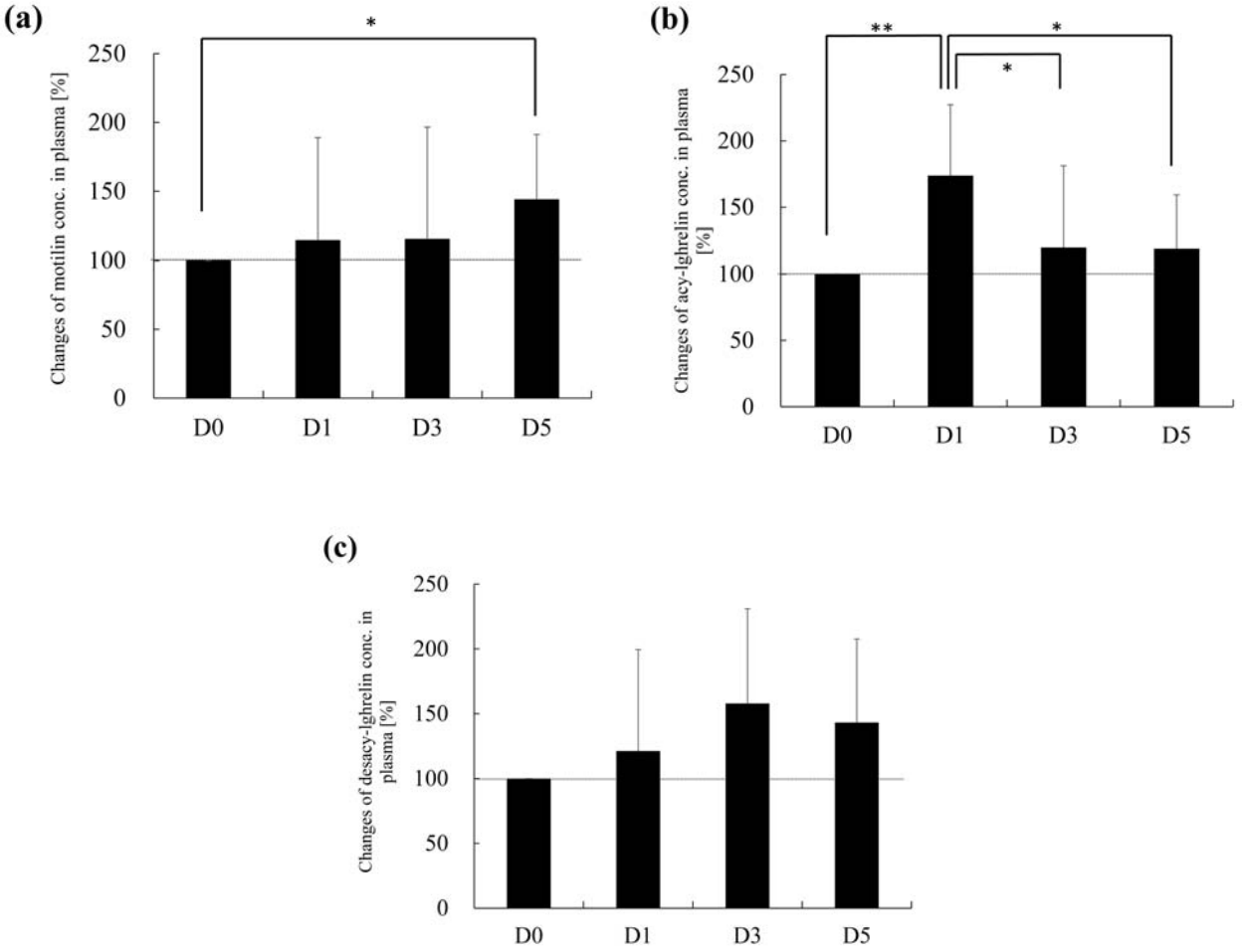

Figure 1. Changes in plasma motilin (a), acyl-ghrelin (b), and desacyl-ghrelin (c) concentrations during the 5 days after surgery (n = 11). Each column represents the mean ± S.D. of plasma GI peptide concentrations as relative values (%) to day 0. **P < 0.01 or *P < 0.05 shows a significant difference compared with each day.

significantly lower than those on day 1 (P = 0.0425, 120.1 ± 61.1% at day 3; P = 0.0375, 119.2 ± 40.1% at day 5, respectively).

3.3. The correlation between plasma gastrointestinal peptide concentrations and gastrointestinal motility

Figure 2 shows the plasma GI peptide concentrations after surgery in both the GI responder and nonresponder groups. The plasma motilin concentrations in the GI responder group significantly increased on day 5 (166.1 ± 44.4%) compared with the nonresponder group (108.6 ± 18.8%) (Figure 2a). The plasma acyl-ghrelin and desacyl-ghrelin concentrations in the GI responder group showed no changes (Figure 2b, c).

4. DISCUSSION

In critically ill patients, there is a disorder of stomach and small intestine movements, slowing gastric emptying. The major pathophysiological mechanisms for delayed gastric emptying in critically ill patients include motor dysfunction in the gut, a lack of coordination between the fundic and pyloric regions of the stomach, feedback inhibition from the adjoining small intestine, or a mix of any of these [12]. The more severe the illness, the higher the chances are for delayed gastric emptying, making it a common occurrence in clinically ill patients [13]. In recent years, changes in plasma GI peptide concentration have been considered the cause of GI hypofunction in clinically ill patients [14-17]. At present, only

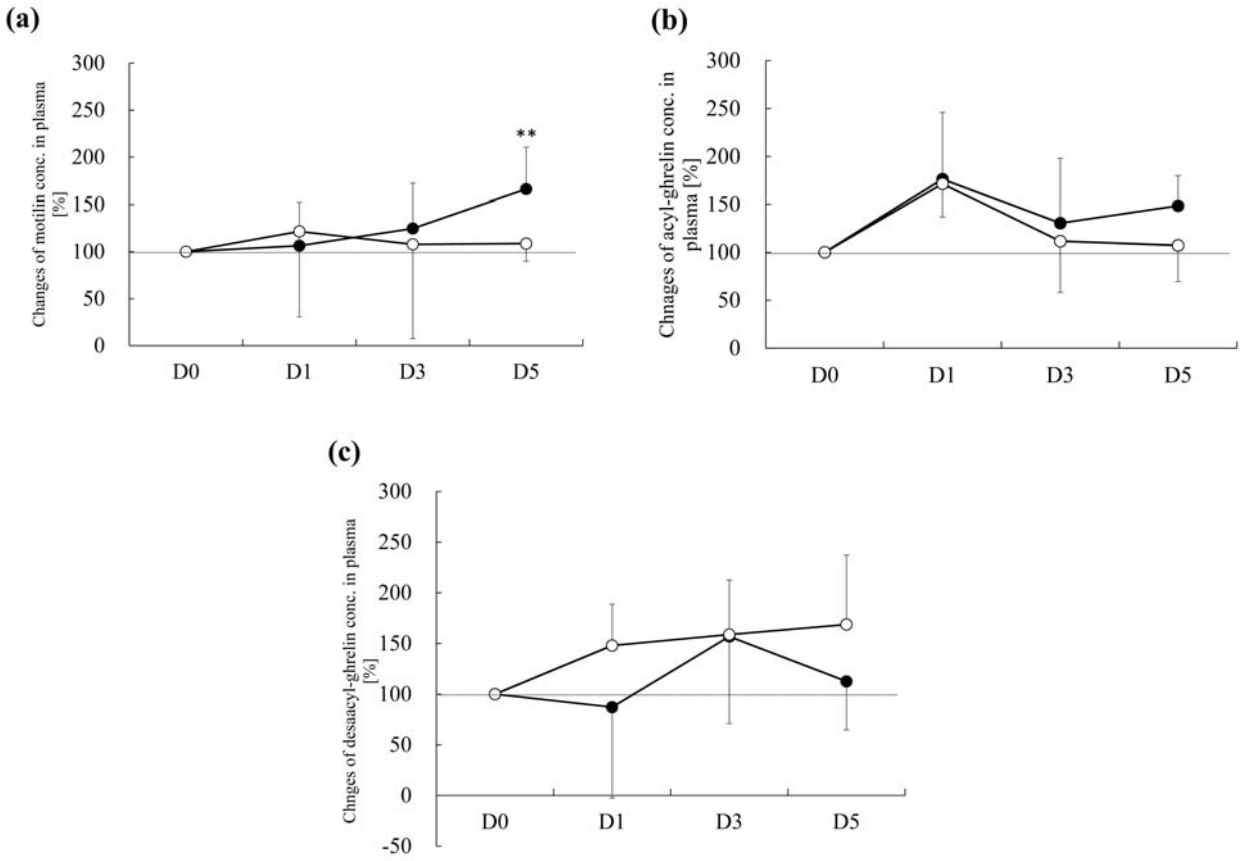

Figure 2. Changes in plasma motilin (a), acyl-ghrelin (b), and desacyl-ghrelin (c) concentrations during the 5 days after surgery for the GI responder and nonresponder groups. Each point represents the mean ± S.D. of the responder group (n = 5: ●) and the nonresponder group (n = 6: ○). Each point represents the mean ± S.D. of plasma GI peptide concentrations as relative values (%) to day 0. **P < 0.01 shows a significant difference comparing the responder and nonresponder groups.

a few reports have examined the relationship between GI motility and peptides after surgery. A purpose of this study was to analyze whether the measurement of plasma GI peptide concentrations might lead to finding a strong relationship with GI motility.

Motilin regulates interdigestive gastrointestinal motility in humans [18]. Plasma motilin shows a cyclic fluctuation during the interdigestive state, and its peak is highly associated with gastric phase III contractions that stimulate gastric emptying. Used as an antibiotic, erythromycin, which is a motilin receptor agonist, can stimulate GI motility and is more effective when given intravenously [19]. Ghrelin is secreted from the stomach when fasting and promotes feeding. In addition, signals are transmitted to the brain from the peripheral nervous system to suppress energy consumption and maintain energy balance [20, 21]. Ghrelin affects the digestive system and promotes the secretion of gastric acid and gastric emptying. The plasma acyl-ghrelin concentrations increase before meals, reach a peak at the start of a meal, and decrease to basal levels within one hour after a meal. Plasma acyl-ghrelin concentration varies by measurement method (e.g., enzyme immunoassays, high-performance liquid chromatography), and it is difficult to evaluate only its values [22-24].

For these reasons, we assessed the changes in the plasma level of acyl-ghrelin on day 0 immediately after surgery. Desacyl-ghrelin does not bind to GHSR, which is known to be its inactive form. When acyl-ghrelin is transformed into de-octanoyl

by butyrylcholinesterase, desacyl-ghrelin is formed [25]. In this study, the plasma concentration of acyl-ghrelin was found to have significantly increased on day 1, followed by an increase in plasma motilin concentration on day 5. Ghrelin is secreted from the stomach, while motilin is released from the duodenum. Furthermore, ghrelin inhibits the release of motilin, whereas motilin decreases plasma ghrelin concentrations [26, 27]. It was thought that the secretional abilities of ghrelin and motilin showed a negative correlation in the GI tract. In the critically ill, the plasma concentrations of acyl-ghrelin decrease in patients with a feeding intolerance, and reduced acyl-ghrelin concentrations are related to delayed gastric emptying. Studies in humans have indicated that both acyl-ghrelin and motilin accelerate the gastric emptying of solid meals, but not liquid fat. The early initiation of enteric nutrition, within 24-48 hr, is recommended in critical care settings, as it is important in maintaining structural and functional intestinal integrity [28]. In this study, all patients were supplied nourishment *via* enteral feeding (liquid) without oral intake within 24-48 hr after surgery. No correlation was found in the change of acyl-ghrelin and motilin concentrations in either the presence or absence of enteral feeding.

In this study, plasma acyl-ghrelin concentrations in the GI response group did not increase in comparison with the nonresponse group. Acyl-ghrelin plays an important role in regulating feeding behavior [29]. Plasma acyl-ghrelin concentrations are increased by 31% after 12 hr fasting and reduced by 22% immediately after habitual feeding in healthy humans [30]. There have been few positive reports of the gastrokinetic ability of acyl-ghrelin; for example, intravenous injections of acyl-ghrelin did not stimulate gastric emptying, whereas they elicited the release of growth hormone [10]. Conversely, motilin infusion elicits gastric phase III contractions in humans [31]. Thus, it is well accepted that released motilin is responsible for gastric phase III contractions in humans. Our current study also showed that plasma motilin concentrations in the GI response group significantly increased compared with the GI nonresponse group, indicating that defective motilin release may play a part in the pathogenesis of the GI dysmotility. We expected that humoral motilin concentrations might instead be a direct measurement of GI dysfunction after surgery.

In recent years, treatment of GI dysfunction that targets the GI peptide has been developed. Erythromycin, which is a macrolide derivative antimicrobial agent, binds to the receptor on the motilin-secretory cells of the upper gastrointestinal tract and promotes gastric emptying. Erythromycin has been shown to improve GI motility after digestive tract surgery [19]. It is reported that the Kampo medicine, a Japanese traditional medicine, improves various GI dysfunctions by adjusting the secretions of GI peptides. For example, daikenchuto increases motilin secretion and has an effect for the prevention of postoperative paralytic ileus and opioid-induced constipation [32]. In this study, it was found that the index of the digestive tract function in postoperative patients was associated with a change in motilin. Furthermore, motilin is associated with not only digestive organ function but also the adjustment of fat metabolism, carbohydrate metabolism and cognitive function [21]. The development of a treatment focused on motilin might be necessary.

There are some limitations to this study. Although this is a pilot study on a small number of patients from a single center, it is possible that GI peptide concentrations could be changed by anesthesia procedures. This study performed an evaluation of GI motility by palpation and auscultation by the practitioner. However, these results suggest that motilin may be responsible for the patient's GI motility improvement. As far as we know, this is the first study of its kind to report on the relationship between GI motility and plasma GI peptides in clinically ill patients; therefore, our findings are important clinically and are a useful method for evaluating GI motility. Further studies are required to establish the role of motilin in acute illnesses.

5. CONCLUSION

A significant difference in motilin changes was observed between the GI response and nonresponse patient groups, suggesting that the plasma concentration of motilin was correlated with gastrointestinal motility after otolaryngological surgery. These results might suggest that motilin could be an index reflecting GI motility after otorhinolaryngological surgery.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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