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Original Article

Modulation of tube feeding protocol to prevent aspiration pneumonia in gastroesophageal reflux

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ARTICLE INFO

Article history:

Received 11 February 2022

Accepted 14 May 2022

Available online 20 May 2022

Keywords:

Gastroparesis

Gastroesophageal reflux

Delayed gastric emptying

Aspiration pneumonia

Tube feeding

SUMMARY

Background & Aims: Aspiration pneumonia, as an enteral tube feeding-related complication, interferes with nutritional administration, and gastroesophageal reflux (GER) is a well-known cause of this problem. One of the factors that induces GER and other abdominal symptoms is gastroparesis, which is a syndrome caused by delayed gastric emptying (DGE) without mechanical obstruction.

High-viscosity formulas are reportedly effective in suppressing GER, and there are new formulas that further increase viscosity and change phase from liquid to semisolid in the stomach, which can be used even with small-diameter tubes such as nasogastric tubes. The management of gastroparesis is useful for preventing aspiration pneumonia. To achieve this, post-pyloric feeding has been recommended, but this needs additional skill and facilities. An elemental diet can hasten pyloric transit and decrease GER, but has less tolerability due to diarrhea. A new nutritional liquid formula containing ingredients fermented by lactic acid bacteria has been introduced and is expected to have rapid pyloric transit (similar to the elemental diet). Thus, this may be useful in the management of GER patients with gastroparesis.

Abbreviations: GER, Gastroesophageal reflux; DGE, Delayed gastric emptying; DPP4, Dipeptidyl peptidase-4.

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<https://doi.org/10.1016/j.nutos.2022.05.004>

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This retrospective study evaluated whether the modulation of nutritional formulas using the new materials contributes to the prevention of tube feeding-related complications such as aspiration pneumonia.

Methods: In patients with tube feeding-related complications, upper gastrointestinal series was performed to assess the gastrointestinal motility. In cases with abnormal motility, we made the modulation of formulas using the aforementioned new types. The effectiveness of the modulation was evaluated by the frequency of aspiration pneumonia, changes in nutritional status and the period of feeding interruption in one year.

Results: Modulation of the tube feeding protocol significantly reduced the incidence of aspiration pneumonia. Tube feeding could be properly continued without any interruption and nutritional status could be recovered and maintained.

Conclusions: Modulation of the tube feeding protocol including the formulas based on gastrointestinal motility status can reduce tube feeding-related complications.

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Introduction

In the nutritional management of elderly patients in particular, respiratory [1,2] and gastrointestinal complications [3–6] are occasionally detected during tube feeding. These complications prevent the continuity of nutrition, and poor nutrition status can worsen prognosis [7]. This is because enteral nutrition has the benefits of maintaining gastrointestinal function (small intestinal villus length, intestinal flora) [8,9], maintaining liver function through the enterohepatic circulation [10–13] and preventing bacterial translocation due to immune breakdown [14].

Aspiration pneumonia is the most common among these respiratory complications; this occurs mainly due to gastroesophageal reflux (GER) [1]. Having a high volume of gastric content and gastric distention caused by delayed gastric emptying (DGE) both lead to relaxation of the lower esophageal sphincter [15,16] and more frequent episodes of GER [6,16,17]. Gastroparesis, which is defined by DGE without mechanical obstruction, is one of the gastrointestinal complications in tube feeding [3–6].

Feeding with high-viscosity formulas is reportedly effective in suppressing GER [18]. In Japan, new formulas that further increase viscosity and can change phase from liquid to semisolid depending on the stomach pH are available; these can be given even through smaller-diameter tubes to prevent GER.

For the management of gastroparesis, slower feeding into the stomach and post-pyloric feeding (wherein the formula is delivered directly into the duodenum or jejunum) are recommended in some publications, including the guidelines published by the American College of Gastroenterology (ACG) [19–21]. However, because post-pyloric feeding is associated with technical difficulties and additional facilities, there is a need to develop easier alternatives. An element diet can hasten pyloric transit and decrease aspiration [22], but this may be less tolerable due to its side effect of diarrhea which is mentioned in its interview form and a literature [23]. Recently, a new nutritional liquid formula containing ingredients fermented by lactic acid bacteria and a digestive liquid food containing whey peptide have been commercially introduced in Japan. A formula using ingredients fermented by lactic acid bacteria is mildly acidic and does not gel when mixed with gastric acid; thus, this is thought to be associated with fast pyloric transit due to its liquid state. Furthermore, the proteins in this formula have been adjusted to contain finer molecules. Because these new formulas are expected to have rapid pyloric transit like the elemental diet, they may be useful in the management of GER patients with gastroparesis.

In this study, we retrospectively evaluated whether the modulation of the nutritional formulas using these new materials can prevent tube feeding-related complications such as aspiration pneumonia.

Patients and methods

A total of 48 patients admitted to our hospital were enrolled in this study. Patients with the following symptoms during tube feeding underwent upper gastrointestinal (upper GI) series for the evaluation of gastric motility: fever, increased sputum, wheezing, nausea, vomiting, gastric distension, and increased gastric drainage after infusion. We compared the clinical data of patients before and after modulation, among those who could be followed up as inpatients at least one year before and after modulation.

Selection criteria

We selected cases that fulfilled both of the following criteria:

1. Patients managed by tube feeding for more than one year before the modified protocol was introduced after the upper GI series.
2. Patients who were maintained on NG tube feeding and followed up clinically for at least one year before and after the protocol introduction.

Patients who did not fulfill the above criteria were not included in the statistical analysis.

Observation period

This was a retrospective cohort study with a two-year observation period, spanning from one year before and after introducing the protocols.

Diagnosis of GER

The diagnosis of GER was defined as the presence of cardia reflux on upper GI series, including remarkable reflux into the esophagus (Fig.1a), the blunting of the His angle (Fig.1b) and the finding of a small amount of contrast reflux, which we called a beak sign (Fig.1b).

In GER patients, an upper GI series does not always have remarkable reflux findings as shown in Fig. 1a; even a small amount of GER with cough reflex during tube feeding can be diagnosed as GER.

Detection of aspiration

To detect aspiration, the qualitative test of applying glucose oxidase test strip to the tip of the oral or intratracheal suction tube was performed. When aspiration is suspected during tube feeding, we used urinary test paper via the glucose oxidase method to detect sugar in the oral and tracheal secretions [24]. The test paper is applied to the tip of the tube after suctioning the oral cavity or tracheostomy. The formulas used had 14.3% YH®, 25.8% Meiflow® and 12.2% Meiflow RHP® of glucose and had quite a high sensitivity for detecting even mild regurgitation. If the sugar was positive with suspicious symptoms of respiratory infection such as fever and/or cough, the patient was kept fasting.

Diagnosis of DGE

DGE was signified by the clinical symptoms of nausea, vomit, and/or over 100 ml of residual contents in the stomach (17% of injection volume).

The diagnosis was confirmed when gastric peristalsis did not occur despite sufficient stretching of the gastric wall after injecting 100 ml of contrast medium and 100 ml of air into the stomach

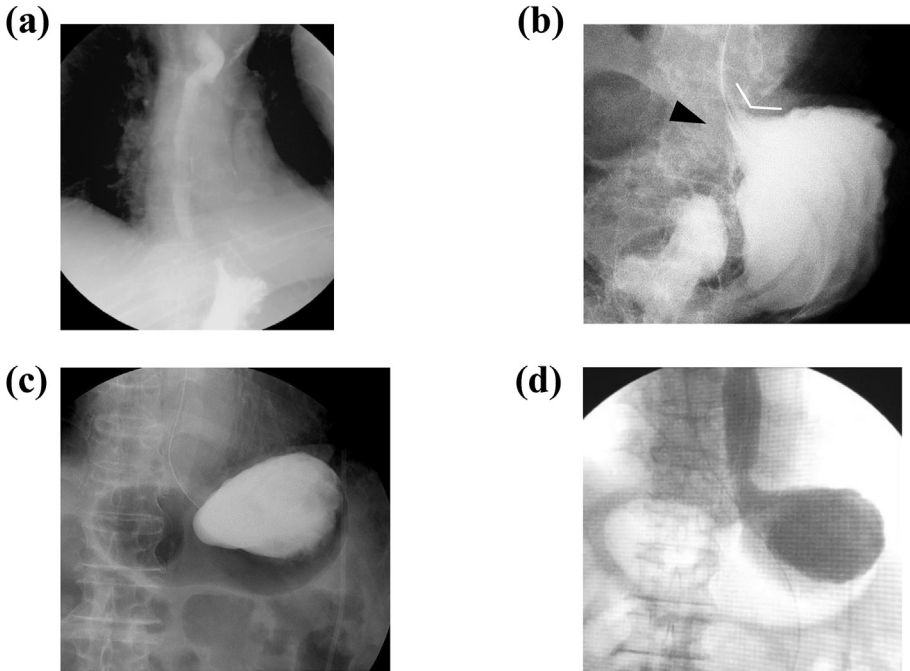


Fig. 1. Representative findings of gastroesophageal reflux (GER) and delayed gastric emptying (DGE) in upper gastrointestinal series. (a) GER without DGE: remarkable regurgitation into the esophagus when injecting 100 ml of contrast medium (3-fold diluted Gastrografin®) via gastrostomy. (b) GER without DGE: a small amount of reflux after 100 ml of infusion, demonstrating the beak sign (black arrow). The His angle was blunt (white angulated line). (c) DGE: poor motility (less than 3Hz) and stagnation of 100 ml of the contrast medium (3-fold diluted Gastrografin®) with an additional 100 ml of air added after injecting contrast medium. (d) GER with DGE.

(total intragastric volume > 200 ml) during the upper GI series (Fig.1c). In some cases, there was reflux of contrast medium into the esophagus due to poor gastric emptying without normal peristalsis (Fig.1d). Additionally, in this study, cases with gastric emptying time > 120 min, gastric peristalsis < 3 Hz on upper GI series, and clinical evidence of vomiting or increased gastric drainage are defined as DGE.

Parameter of nutritional status

For the long-term evaluation of nutritional status, we evaluated the value of serum albumin and body weight. Because most of our patients were bedridden, their muscle mass was not expected to increase.

Protocol before the modulation

Before modulation, the standard regimen at our hospital was as follows: Meibalance 1.5® (Meiji Co., Ltd., Tokyo, Japan, 400 kcal/267 ml or 500 kcal/333 ml) 3 times a day (at 5 am, 11 am, and 5 pm) with 600 ml in volume after dilution by water, given for 30–60 minutes. This was the dextrin-based liquid food. This formula had a viscosity of 35 mPa · s, pH of 6.6, and osmotic pressure of 590 mOsm/l. The feeding tube was clumped for two hours after the administration. Afterwards, the residual volume in the stomach was evaluated by de-clumping and drainage through the nasogastric (NG) tube.

Modulation of the feeding

We modulated the standard formulas according to each patient's diagnosis suggested by the upper GI series.

For patients with GER, nutrient was changed to a formula which further increases viscosity and changes the phase from liquid to semisolid by the acidity in the stomach (Fig. 2). According to the manufacturer, the viscosity increases from 400 mPa · s to 4000 mPa · s in the stomach. This formula could be administered through small-diameter tubes (10–12 Fr.), supported by the pressurized holder provided by the manufacturer. It had several types of packages of various volumes and calorie contents. Specifically, these were Meiflow® (300 kcal/167 ml, 400 kcal/223 ml) and Meiflow RHP® (500 kcal/578 ml) (Meiji Co., Ltd., Tokyo, Japan). We used a combination of these packages depending on the patient's body size and requirements.

In Japan, 10-times diluted vinegar (containing acetic acid) is used for tube flushing to prevent NG tube occlusion, as justified by the study of Saijo [25]. Among elderly patients, gastric acidity is relatively weak, and thus the viscosity of the formula does not sufficiently increase. Therefore, in this study, to promote gelation of the formula in the stomach, 30 ml of the diluted vinegar was administered into the stomach prior to administering the formula. After infusion of the formula, 10 ml of the same vinegar was infused again for better gelling in the stomach and to flush the tube. Through this method, a total of 120 ml/day of diluted vinegar is used for each patient; this volume does not exceed the typical intake of ordinary Japanese people.

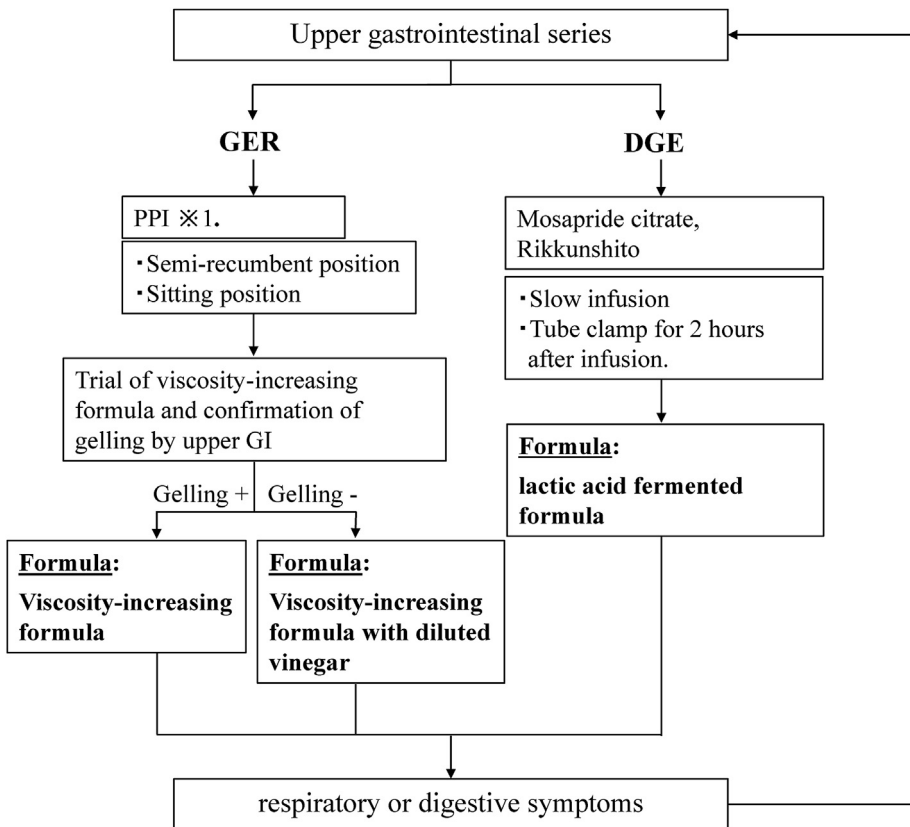


Fig. 2. Modulated tube feeding protocol. ×1. If there is no exacerbation of gastroesophageal reflux disease without proton pump inhibitor (PPI) therapy, PPI therapy is canceled to increase the viscosity of the formula which can change phase depending on the pH of gastric acid.

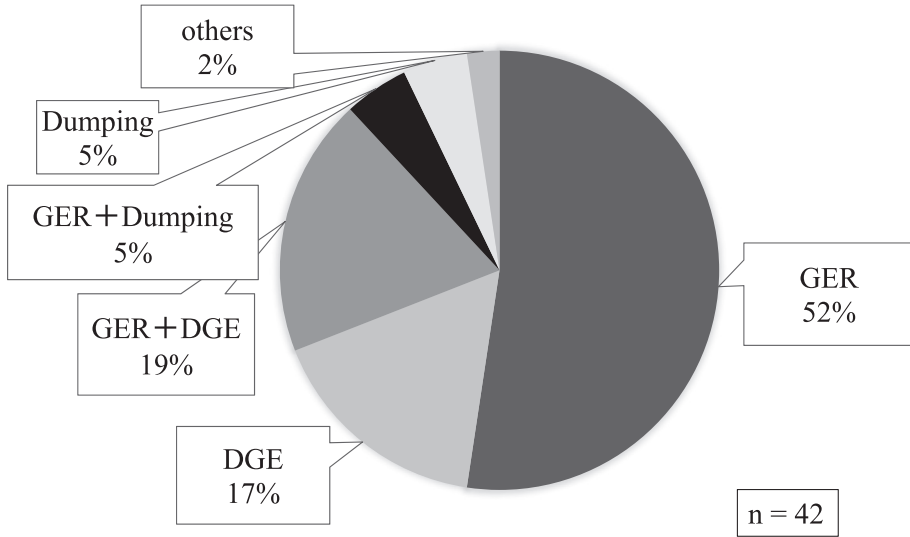


Fig. 3. Causes of tube feeding-related complications. Among patients with enteral tube feeding-related complication in our hospital, 76% (n = 32) had gastroesophageal reflux (GER) disease, while 36% (n = 15) had delayed gastric emptying (DGE) on upper gastrointestinal series. Both GER and DGE were present in 19% (n = 8) of cases.

For the treatment of confirmed DGE, we used a liquid formula containing ingredients fermented by lactic acid bacteria (YH®) (Fig. 2). This formula is mildly acidic and does not gel when mixed with gastric acid, and is theoretically associated with high pyloric transit due to its liquid state. This new formula was administered slower than before, over a span of 1–2 hours. The total amount of liquid per meal was also adjusted to 600 ml, which included YH® (400 kcal/400 ml) (Meiji Co., Ltd., Tokyo, Japan) and 200 ml of water. The frequency and interval of feeding were unchanged.

For one year, we evaluated the effectiveness of this modulation, based on the frequency of aspiration pneumonia, changes in nutritional status, and fasting period due to the complications. The number of days of antibiotic therapy was also assessed.

We statistically analyzed the number of cases for which long-term and sufficient clinical information before modulation was available.

Statistical analysis

In this study, we collected all data retrospectively. Data are presented as mean \pm standard deviation. Student's t-test was used for parametric data when two means were compared. Statistical significance was set at *P* value <0.05.

Statement of ethics

This study was approved by the ethical committee of the Japan Medical Association (#R2-18).

Human rights

All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent

Written informed consent was obtained from all patients for being included in the study.

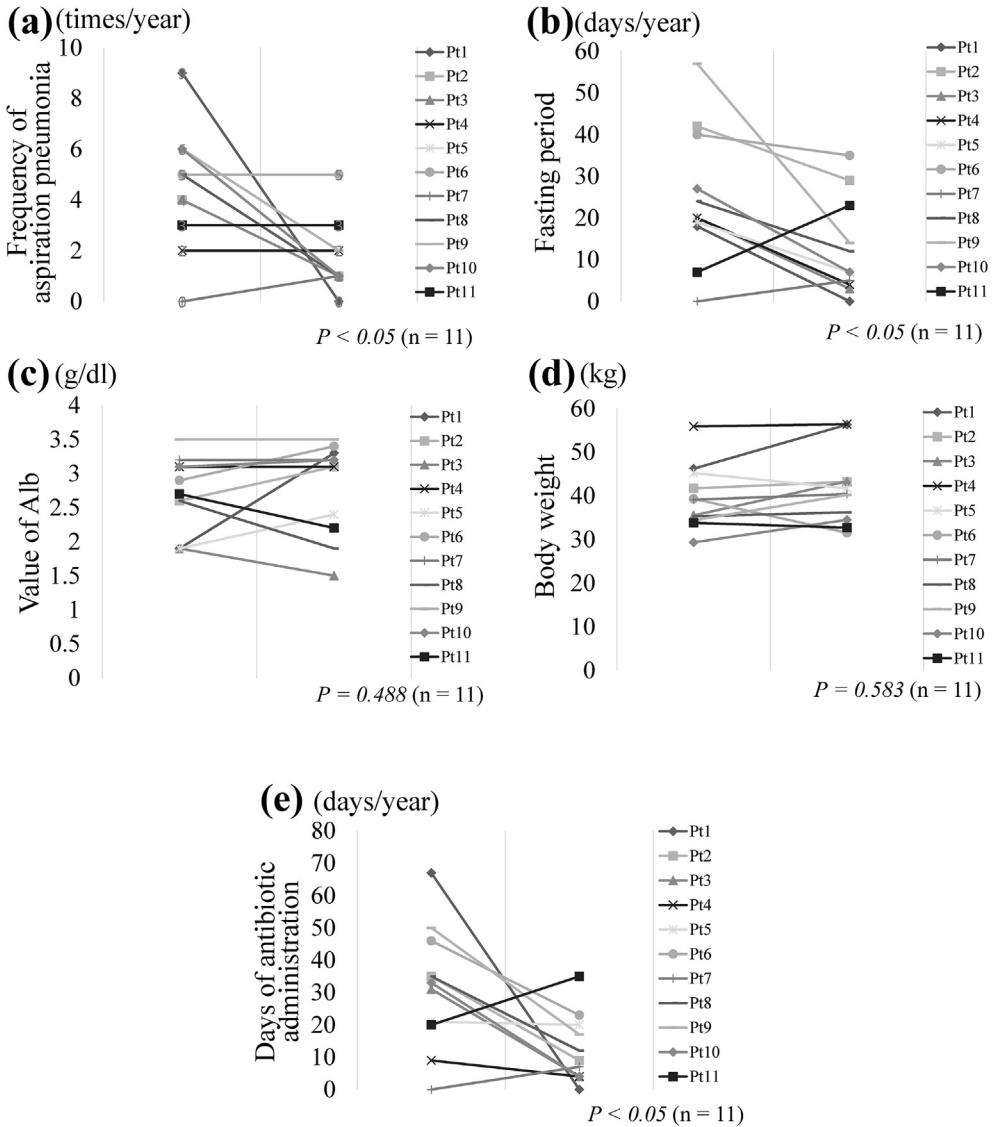


Fig. 4. Changes in clinical parameters by modulation of the tube feeding protocol. (a) The incidence of aspiration pneumonia decreased significantly from 4.27 ± 2.37 to 1.82 ± 1.40 times/year after modulation ($P = 0.022$, $n = 11$). (b) The length of fasting periods due to any complication was shortened significantly from 24.91 ± 16.21 to 12.64 ± 11.52 days/year after modulation ($P = 0.021$, $n = 11$). (c) The value of serum albumin tended to increase from 2.67 ± 0.56 to 2.8 ± 0.68 g/dl ($P = 0.488$, $n = 11$). (d) Body weight tended to increase from 39.6 ± 7.40 to 41.5 ± 8.39 kg ($P = 0.583$, $n = 11$). (e) For treatment of aspiration pneumonia, the average length of antibiotic treatment in a patient (mean \pm S.D.) decreased significantly from 31.55 ± 18.92 to 12.27 ± 10.53 days per year ($P = 0.018$, $n = 11$).

Table 1
Characteristics of the study patients

	Age (y.o.)	Sex	Disease at admission	Upper GI	Abdominal surgery	Route of administration	PPI
Pt 1	64	M	subarachnoid hemorrhage, diabetes mellitus	GER, DGE	–	NG tube	-
Pt 2	97	F	dysphagia, aspiration pneumonia	GER, DGE	gastrostomy	gastrostomy	+
Pt 3	75	M	aspiration pneumonia, diabetes mellitus	GER, DGE	–	NG tube	-
Pt 4	88	M	cerebral infarction, aspiration pneumonia, epilepsy	GER, DGE	–	NG tube	+
Pt 5	79	M	Parkinson's disease, aspiration pneumonia	GER, dumping	–	NG tube	-
Pt 6	77	F	Parkinson's disease, epilepsy	GER, DGE	gastrostomy	gastrostomy	+
Pt 7	98	F	traumatic subarachnoid hemorrhage, AF, diabetes mellitus	GER	–	NG tube	-
Pt 8	91	F	cerebral infarction, AF	GER, DGE	–	NG tube	+
Pt 9	94	F	Parkinson's disease, ischemic heart disease, breast cancer	GER, DGE	–	NG tube	-
Pt 10	99	F	dysphagia, dementia	GER, DGE	–	NG tube	-
Pt 11	79	M	aspiration pneumonia, dysphagia	GER, dumping	gastrectomy (Billroth-I)	NG tube	-

AF, atrial fibrillation; NG tube, nasogastric tube; PPI, proton pump inhibitor.

Table 2
Adapted protocol for patients with delayed gastric emptying

	Protocol	Reason for re-selecting the protocol	Frequency of pneumonia (times) before protocol/after protocol
Pt 1	DGE protocol	–	9/0
Pt 2	DGE protocol	–	4/1
Pt 3	DGE protocol	–	4/1
Pt 4	DGE protocol (7 months) → GER protocol (5 months)	Due to finding of upper GI: GER without DGE	2/2
Pt 6	DGE protocol	–	5/5
Pt 8	GER protocol (8 months) → DGE protocol (1 month) → GER protocol (3 months)	Due to complications of DGE when UTI occurred.	5/1
Pt9	DGE protocol	–	6/2
Pt 10	DGE protocol	–	6/1

UTI, urinary tract infection.

Result

Among 42 patients (mean age: 86.21 ± 9.4805, range: 62–100 years) with symptoms that warranted evaluation via upper GI series, 76% had GER and 36% had DGE (Fig. 3).

Statistical analysis was performed on the 11 cases (mean age: 85.55 ± 11.44, range: 64–99 years) who met the selection criteria of this study (Table 1). All patients were hospitalized during observation period.

Among those on the modulated feeding protocol, aspiration pneumonia was significantly reduced (Fig. 4a, *P* < 0.05, Student's *t*-test), and the fasting period was significantly shortened (Fig. 4b, *P* < 0.05, Student's *t*-test). Thus, nutritional status could be maintained and even improved with fewer fasting

periods (Fig. 4c, 4d). Since the incidence of aspiration pneumonia was reduced, the frequency of antibiotic administration also decreased significantly (Fig. 4e, $P < 0.05$, Student's *t*-test).

In 8 cases, DGE was observed during the 2-year observation period before and after the protocol modulation (Table 2). Among these, 7 patients had both GER and DGE from the beginning before the protocol modulation. Notably, one of them was shifted to the GER protocol in the middle of the study because the repeated upper GI series did not show DGE.

Another patient was initially managed using the GER protocol because he had GER without DGE, but was then temporarily shifted to the DGE protocol because he developed DGE transiently complicated with GER during a urinary tract infection. After the urinary tract infection was cured and DGE findings were no longer observed on upper GI series, the patient was returned to the GER protocol management.

Discussion

GER is widely known as one of the risk factors for aspiration pneumonia [8,9]. Generally, to prevent aspiration pneumonia in a patient maintained on NG tube feeding, a high-viscosity formula has been recommended [18].

In this study, we used two types of new formulas. One included a viscosity-increasing content allowing it to change phase from liquid to semisolid in the stomach due to its acidity, and this had a greater advantage in GER-dominant cases. The other was a liquid formula containing ingredients fermented by lactic acid bacteria, which we hypothesized to have better pyloric transit. This was used in a patient with both GER and DGE (wherein DGE was more dominant). Using this formula, the incidence of aspiration pneumonia was reduced significantly in both GER and DGE.

The viscosity-increasing formula we used in our GER protocol had a viscosity of over 400 mPa · s, which increases up to 4000 mPa · s in the stomach. In contrast, the regular formula had a viscosity of 35 mPa · s, which might have contributed to the suppression of reflux. When we examined the intragastric dynamics of this new formula using upper GI series, a small amount of regurgitation, as evidenced by the presence of the “beak sign,” was also suppressed. Notably, even before gelation in the stomach, its viscosity can be as high as 400 mPa · s. Therefore, the use of a pressurized holder is necessary for its administration through a small-diameter tube, but the handling was still easy.

On the other hand, the liquid formula containing ingredients fermented by lactic acid bacteria had a pH of 4.0. This was adjusted to be more acidic than the regular formula, which has a pH of 6.6. The low pH and low molecular weight due to the fermentation by lactic acid bacteria are thought to contribute to gastric clearance without gelation in the stomach. The use of this formula completely eliminated the episodes of aspiration pneumonia in a diabetic gastroparesis patient. This patient regularly suffered from aspiration pneumonia nine times a year when the standard enteral formula was being used. Because there were no interruption of feeding and no exhaustion of protein without aspiration pneumonia, this might have led to the healing of a severe bed sore that had been difficult to treat. However, in cases of DGE associated with Parkinson's syndrome, the modulation of nutritional formula could not prevent aspiration pneumonia, and a change from intragastric administration to post-pyloric administration was considered necessary.

From a physiological point of view on gastric emptying, peristalsis occurs in a cycle of approximately 3 Hz (3 times/minute); gastric emptying time is said to last 20–30 min for the solid component and more rapidly for the liquid component [26]. Furthermore, Yamoto *et al.* reported that the half-time of gastric emptying was significantly longer with a semisolid formula (60 minutes) versus a liquid formula (30 minutes) [27].

Gastroparesis commonly occurs as a complication of diabetes mellitus (29%) and after gastric surgery (13%) [4]. However, in many cases, the underlying cause is not identified, thus being termed as idiopathic gastroparesis (36%) [4]. In this study, DGE was found in 8 out of 11 cases over a follow-up of 2 years, among which 2 patients had diabetes mellitus. Regarding postsurgical DGE, two patients in this study had undergone gastrotomy, and idiopathic gastroparesis was found in 4 cases. In one case, DGE without any clinical symptoms except GER could be diagnosed only by upper GI series, and thus, it should be considered that DGE could be the primary cause of GER.

In this study, 36% of the patients had DGE during upper GI analysis ($n = 42$); the literature indicates that DGE can occur idiopathically [4]. However, the factor of age in this study can be a risk factor leading to a slower gastric emptying process [21]. In short, the presence of DGE should be considered in the selection of nutritional material.

Regarding patients with hypoalbuminemia despite a decreased (or unchanged) incidence of aspiration pneumonia, these can be attributed to the exhaustion of protein due to repeated urinary tract infections, increased protein requirements due to complications of bedsores, and dumping syndrome with malabsorption syndrome after gastrectomy.

As for the three patients who lost weight, one was a dumping case after gastrectomy. The other two patients had Parkinson's syndrome, which is commonly prone to complications of DGE [28]. In those patients, intragastric feeding failed to reduce the incidence of aspiration pneumonia. Thus, post-pyloric administration should be considered for such cases wherein aspiration pneumonia cannot be prevented [17,19].

A key takeaway of our study is that, in order to prevent aspiration pneumonia, formula selection in tube feeding should be determined based on the primary risk factor (i.e., GER or DGE) present.

In conclusion, nutritional formulas should be tailored to the presence of comorbidities relating to upper gastrointestinal motility. The correct choice of formula can reduce the risk of aspiration pneumonia during the duration of nutritional management.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Statement of authorship

Masataka Sakisaka worked as a doctor in charge for the patient and a corresponding author, and he was also the chief investigator of this clinical study. He designed the study, analyzed the data, and wrote the draft of this article.

Daiki Yoshii also worked as a co-physician in charge of the patient, and supported the acquisition and the analysis of the data. He revised the article.

Masaaki Sakisaka worked as a hospital manager and contributed to the conception and design of the study. He interpreted the data and revised the article.

Yukihiro Inomata is the last author and has made contributions to the conception and design of the study. He worked for the analysis and interpretation of the data, as well as revised the draft of the article.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Masataka Sakisaka has had a one-year consultant contract with Meiji Co., Ltd. Since April 1, 2021 and was paid USD 2,474 a year as a consultant fee. All other authors declare no competing interests.

Acknowledgements

We would like to extend our most sincere gratitude to our nursing staff and nutritional section staff for their support in the implementation of nutritional management.

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