Jikeikai Med J 2009 ; 56 : 21-30

Basal and Omeprazole-Inhibited Gastric Acid Environment in Patients with Gastric Cancer who Underwent Endoscopic Submucosal Dissection

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ABSTRACT

Background : Proton pump inhibitors are administered to patients with gastric cancer after endoscopic resection. However, the gastric acid environment of these patients has not been examined.

Aim : To examine the gastric pH and its alteration by omeprazole in patients with gastric cancer who undergo endoscopic submucosal dissection (ESD).

Methods : Gastric pH was assessed with a wireless pH monitoring system. Omeprazole was administered intravenously at a dose of 40 mg per day on days 1 and 2 after ESD and administered orally at a dose of 20 mg per day on days 3 and 4 after ESD.

Results : The mean 24-hour pH at baseline was 4.4±2.1 in 20 patients, who were divided into 2 groups on the basis of mean basal pH (6 patients with pH＝6 and 14 patients with pH＜6). Despite treatment with omeprazole, in 6 of the 14 patients with mean basal pH＜6, pH did not increase to ＞6 after ESD. In 5 of these 6 patients in whom acid levels were not suppressed, basal pH values at 9 am were less than 4. In contrast, the pH values were higher than 4 in 13 of 14 patients in whom acid levels were suppressed.

Conclusions : Low-dose omeprazole fails to sufficiently suppress gastric acid after ESD in one-third of patients with gastric cancer. (Jikeikai Med J 2009 ; 56 : 21-30)

Key words : gastric cancer, acidity (intragastric), clinical pharmacology, endoscopy

INTRODUCTION

Endoscopic submucosal dissection (ESD)[1-3] is a new therapeutic method that enables radical *en bloc* resection of large gastrointestinal (GI) neoplasias that cannot be resected with conventional endoscopic mucosal resection[4]. Despite being associated with a higher rate of cure than is endoscopic mucosal resection, ESD frequently results in hemorrhage during or after the procedure[5], primarily because a large mucosal defect remains open[6].

Although acid-suppressing drugs are administered to prevent hemorrhage from ESD-induced gastric ulceration and to accelerate ulcer healing[7], no detailed data are available on the intragastric acid environment of patients with gastric neoplasia, who are usually hypoacidic. Using a long-term wireless pH monitoring system[8], we investigated the basal intragastric pH status and its alteration by a proton pump inhibitor (PPI) in patients with gastric cancer

Received for publication, March 9, 2009
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who underwent ESD.

METHODS

1. Subjects

Patients who underwent ESD for gastric cancer at The Jikei University Hospital from May 2005 through October 2006 were eligible for the present study. The following exclusion criteria were applied: 1) gastric neoplasia located proximal to where the attached pH capsule would come in contact with the ESD-induced ulcer; 2) severe comorbidities, including hepatic, renal, cardiopulmonary, and hematologic disease; 3) age greater than 85 years; 4) previous upper GI surgery or vagotomy; 5) ongoing regular intake of nonsteroidal anti-inflammatory drugs or steroid hormones; 6) ongoing regular treatment with a drug known to interact with omeprazole (e.g., warfarin, diazepam, phenytoin, itraconazole); and 7) history of previous allergy to a PPI.

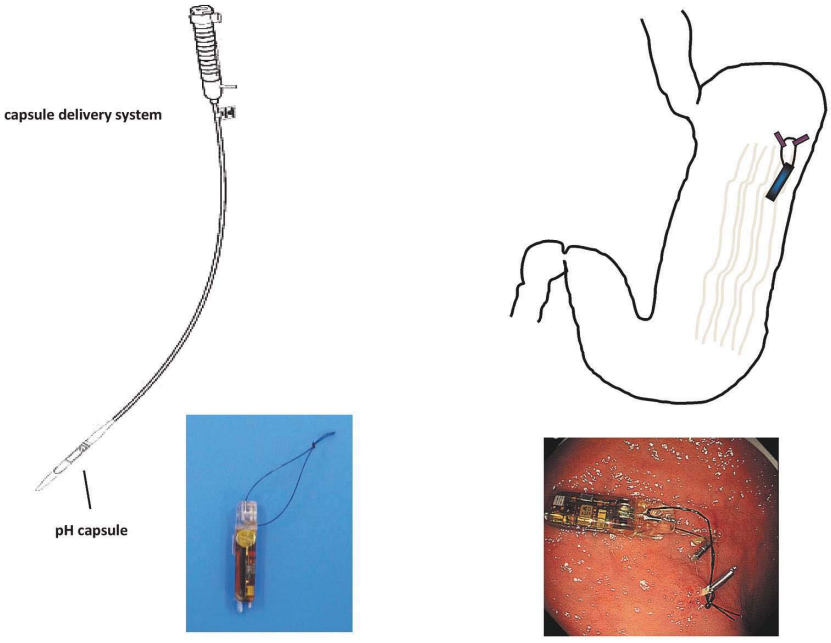
2. Study protocol

Enrolled patients who gave written informed consent were forbidden to use any acid suppressant for 2 weeks before ESD. Patients were hospitalized and fasted, and the Bravo pH capsule (Medtronic, Shoreview, MN, USA)[8] was attached via endoscopy in the morning of the day before ESD. Intragastric pH monitoring was performed consecutively until the fifth hospital day (post-ESD day 4). Patients ate standard hospital meals without any acid suppressant on the day before ESD. On the second hospital day (post-ESD day 1), ESD was performed in the afternoon. From the evening of post-ESD day 1 to the evening of post-ESD day 3, 20 mg of omeprazole was administered intravenously twice a day under conditions of nil per os, and from the morning of post-ESD day 4, 20 mg omeprazole was administered orally once in the morning. Patients started receiving standard liquid meals from the evening of post-ESD day 3 and rice gruel on post-ESD day 4 and post-ESD day 5, respectively. This study was approved by the ethics committee of The Jikei University School of Medicine and was conducted in accordance with the revised Helsinki Declaration (1989).

3. Intragastric pH monitoring

The transmitter capsule, which was detached from the delivery system of the Bravo pH monitoring system (Medtronic), was looped with a 2-0 nylon thread in advance (Fig. 1A). An over-tube was inserted into the esophagus by means of upper GI endoscopy under intravenous anesthesia with meperidine and flunitrazepam. The capsule with the nylon thread loop was endoscopically delivered *via* the over-tube and attached to the greater curvature of the upper gastric corpus with endoscopic clips (Fig. 1B). Data on intragastric pH were recorded wirelessly with the extracorporeal Bravo pH receiver and analyzed with Polygram Net pH testing application software (Medtronic). The basal status of the intragastric acid environment was evaluated from the mean pH and the pH$<$4 holding time (%time pH$<$4) before ESD (pre-ESD day 1: from noon of the first hospital day to noon of post-ESD day 1). Intragastric pH alterations induced by the PPI were evaluated with the above data every 24 hours from 6 pm on post-ESD day 1 to post-ESD day 4. The data are presented as means$\pm$standard deviations (SD). One-way ANOVA was used to compare the baseline and omeprazole-inhibited values. A P-value$<$0.05 was considered to indicate statistical significance.

Because previous studies have suggested that a pH value$=$6 is critical for blood clot stability and rebleeding from a hemorrhagic peptic ulcer[9-12], the enrolled patients were divided into groups with mean basal intragastric pH values on pre-ESD day 1 of $<$6 and $=$6. The %time pH$<$4 is often used as an index for assessing the intragastric acid environment and its alteration by acid-suppressing agents[13]. Intragastric pH environments were tentatively classified as hyperacidic, mesoacidic, and hypoacidic, which were defined as mean %time pH$<$4 of $=$80%, 20% to 80%, and $=$20%, respectively. Twenty-four—hour pH monitoring is not easily performed, but intragastric pH at a proper fixed time is easily measured with standard clinical procedures, such as upper GI endoscopy. Therefore, we analyzed 1) whether a fixed-time pH is correlated with median 24-hour pH, and 2) whether a fixed-time pH can be used to predict the efficacy of acid suppression with omeprazole.



1A 1B

Fig. 1A. The transmitter capsule, which was detached from the delivery system of the Bravo pH monitoring system, was looped with a 2-0 nylon thread in advance.
B. The capsule with the nylon thread loop was endoscopically delivered *via* the over-tube and attached to the greater curvature of the upper gastric corpus with endoscopic clips.

Because upper GI endoscopy is often performed during the morning in fasting patients, 9 am on pre-ESD day 1 with the patient fasting was used as the fixed time for this analysis.

4. Genotyping of P450 CYP2C19

Seventeen of the 20 enrolled patients underwent *CYP2C19* genotyping using polymerase chain reaction-restriction fragment length polymorphism with allele-specific primers for the CYP2C19 wild-type (*1) gene and the 2 mutated alleles, CYP2C19*2 (*2) in exon 5 and CYP2C19*3 (*3) in exon 4.28-30. On the basis of these results, the subjects were classified into the following genotype groups : 1) extensive metabolizers (*1/*1) ; 2) intermediate metabolizers (*1/*2 or *1/*3) ; and 3) poor metabolizers (*2/*2, *3/*3, or *2/*3)[14,15].

5. Indication and procedure for ESD

The indication for ESD is intramucosal gastric cancer (category 4.4 of revised Vienna classification[16]) composed of differentiated adenocarcinoma (intestinal type of adenocarcinoma). In the case of gastric cancer with scar formation, the indication is restricted to adenocarcinoma of less than 3 cm in diameter, and for cases in which there is no scar formation, adenocarcinoma of any size. Circumferential markings were made with brief bursts of cautery with the tip of a Hook knife (KD-620LR ; Olympus Medical Systems, Tokyo, Japan), a few millimeters from the margin of the target lesion. Then, 0.5% sodium hyaluronate in a 10% glycerin solution with 0.025% epinephrine and 0.05% indigo carmine was injected submucosally. A circumferential marginal incision was made a few millimeters outside the marked spots with a needle knife (KD-1L-1 ; Olympus Medical Systems) or the Hook knife using the Drycut mode or the Swiftcoag mode or both of Erbotom Vio (ERBE Elektromedizin GmbH, Tubingen, Germany) or both. Submucosal dissection was then performed with the Hook knife using the Drycut mode or the Swiftcoag mode or both. The ulcer created in this way after resection was carefully examined, and any visible vessels and adherent clots were coagulated with a hemostatic forceps (HDB2418W-W ; Pentax, Tokyo, Japan) in the Softcoag mode.

RESULTS

1. Demographic and clinical characteristics of the subjects

Of the 163 patients with gastric neoplasia who underwent ESD, 20 met the inclusion criteria and were enrolled in the study. The male-to-female ratio was 18 : 2, and the patients had a mean age of 69.3±8.1 years. The mean lesion diameter was 17.2±9.6 mm, and the mean diameter of the excised specimens was 35.4±11.4 mm.

2. Basal intragastric pH environments of patients with gastric neoplasia

The mean basal intragastric pH on pre-ESD day 1 in the 20 patients with gastric neoplasia was 4.38±2.07. Six of the 20 patients (30%) were placed in the group with mean pH=6 (mean intragastric pH, 6.55±0.33), and 14 of 20 patients (70%) were placed in the group with mean pH<6 (mean intragastric pH, 3.44±1.77).

At the basal intragastric pH monitoring on pre-ESD day 1, the mean %time pH<4 of the 20 patients with gastric neoplasia was 38.6±35.1.

Of the 20 enrolled patients, 6 (30%), 8 (40%), and 6 (30%) were placed in the hyperacidic group (mean %time pH<4, 93.75±5.6), the mesoacidic group (mean %time pH<4, 43.78±16.3), and the hypoacidic group (mean %time pH<4, 3.25±7.96), respectively.

3. Alteration of intragastric pH environment by omeprazole

Omeprazole significantly ($p=0.007$) increased the mean intragastric pH of the 20 patients from 4.38±2.07 on pre-ESD day 1 to 5.88±2.10, 6.15±1.64, 6.02±1.49, and 6.12±1.12 on post-ESD days 1, 2, 3, and 4, respectively (Fig. 2A). For the 6 patients with a mean basal intragastric pH=6, the mean pH remained>6 during the post-ESD period (mean pH of 7.37±0.33, 7.25±0.42, 6.85±0.29, and 6.67±1.89 on post-ESD days 1, 2, 3, and 4, respectively). For the 14 patients with a mean basal intragastric pH<6, omeprazole significantly ($p=0.013$) increased the mean intragastric pH. However, the omeprazole-altered mean pH remained<6 during the post-ESD period (mean pH values of 5.20±2.23, 5.42±1.76, 5.47±1.72, and 5.58±1.45 on post-ESD days 1, 2, 3, and 4, respectively ; Fig. 2B). Eight (57%) of the 14 patients with a mean basal intragastric pH<6 showed mean pH increases to >6 during the post-ESD period (mean pH values of 4.74±1.0, 6.91±0.39, 6.98±0.29, 6.68±0.45, and 6.75±0.21 on pre-ESD day 1 and post-ESD days 1, 2, 3, and 4, respectively). However, 6 of 14 patients with a mean basal intragastric pH<6, did not show increases in pH to >6 during the post-ESD period (mean pH values of 1.71±0.64, 3.2±1.68, 4.18±1.33,

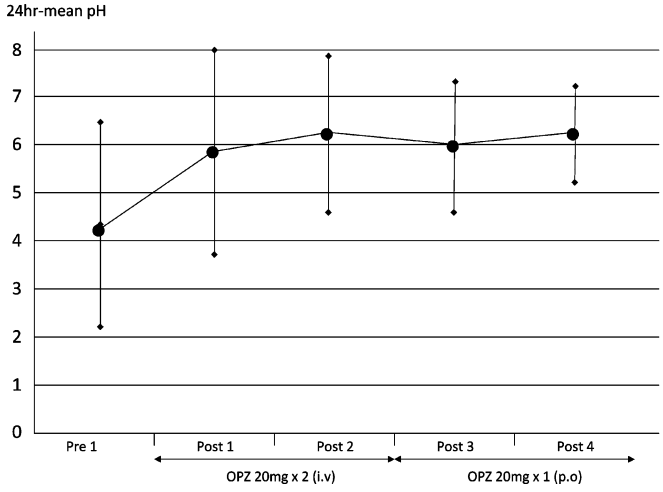


Fig. 2A. Mean intragastric pH of 20 patients with gastric cancer at baseline (pre-ESD day 1) and during the post-ESD period (post-ESD days 1 to 4). Omeprazole (OPZ) significantly ($p=0.007$) increased the mean intragastric pH level.

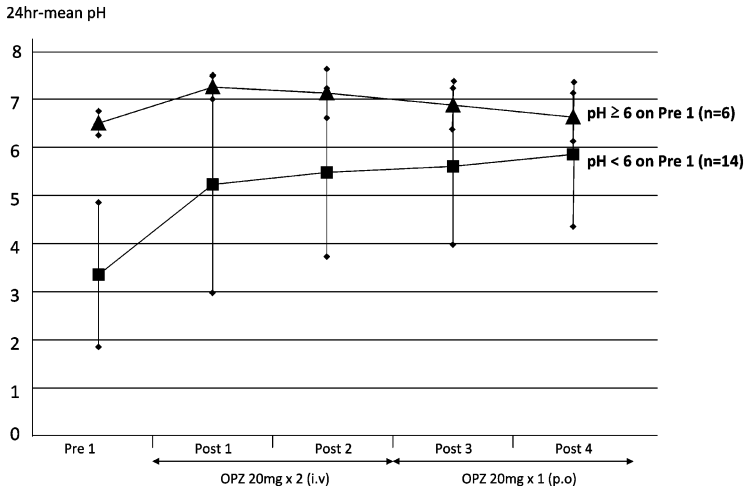


Fig. 2B. Comparison of mean intragastric pH between patients with gastric cancer and mean pH<6 or =6 on pre-ESD day 1. Because previous studies have suggested that a pH≥6 is critical for blood clot stability and preventing rebleeding from a hemorrhagic peptic ulcer, the 20 patients were divided into groups with a mean intragastric pH values of <6 or =6 at baseline (pre-ESD day 1). For the 14 patients with a mean basal intragastric pH<6, omeprazole (OPZ) significantly ($p=0.013$) increased the mean intragastric pH. However, the OPZ-altered mean pH remained<6 during the post-ESD period.

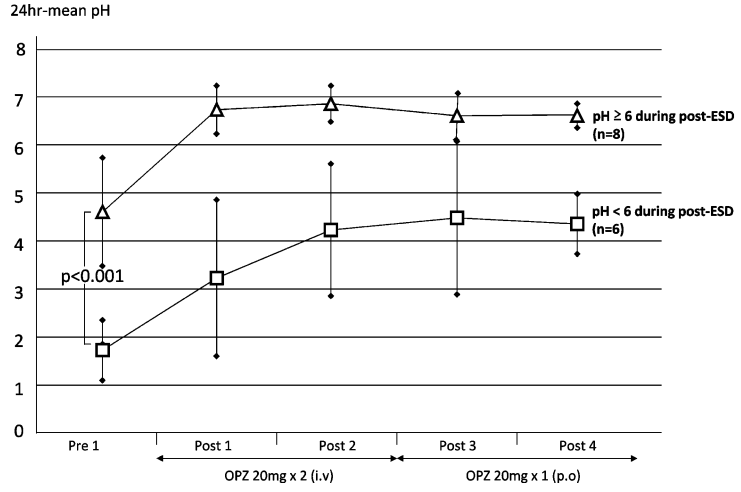


Fig. 2C. Mean intragastric pH of 14 patients with gastric cancer and a mean pH<6 at baseline intragastric pH monitoring on pre-EDS day 1. Eight patients showed mean pH increases to >6 during the post-ESD period. However, 6 patients did not show increases in pH to >6 during the post-ESD period.

4.5±1.77, and 4.4±0.85 at pre-ESD day 1 and post-ESD days 1, 2, 3, and 4, respectively ; Fig. 2C). The mean basal intragastric pH of the 6 patients who had a mean pH<6 during the post-ESD period was significantly ($p<0.0001$) lower than that of the 8 patients who had a mean pH=6 during the post-ESD period (Fig. 2D).

CYP2C19 genotyping showed that 2 and 4 of the 6 patients who had a mean pH<6 during the post-ESD period were extensive metabolizers and intermediate metabolizers, respectively, and no poor metabolizers were found in this group. The other 14 patients who had a mean pH<6 during the post-ESD period, 5, 2, and 4 patients were extensive metabolizers, intermediate metabolizers, and poor metabolizers, respectively. The mean pH of the 2 patients who were extensive metabolizers remained <4 during the post-ESD period despite omeprazole administration.

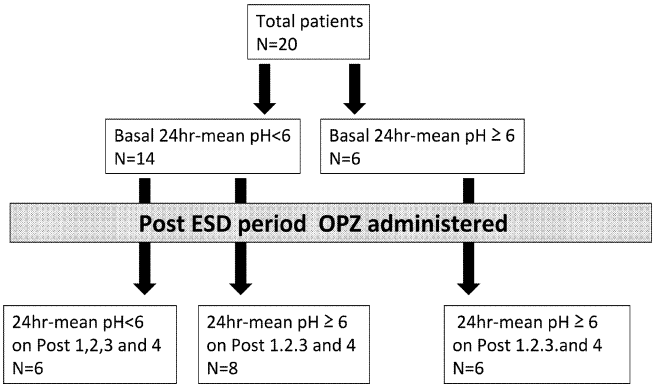


Fig. 2D. Flowchart of mean 24-hour pH in 20 patients before and after ESD.

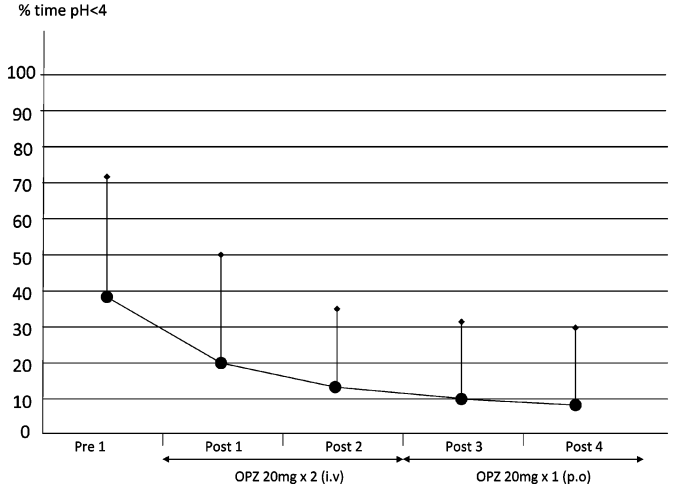


Fig. 3A. Mean %time pH<4 of the 20 patients with gastric cancer at baseline (pre-ESD day 1) and during the post-ESD period (post-ESD days 1 to 4). Omeprazole (OPZ) decreased the mean %time pH<4.

Omeprazole significantly ($p<0.001$) decreased the mean %time pH<4 of all patients from 38.6±35.1 on pre-ESD day 1 to 20.1±33.1, 13.3±24.8, 10.5±24.9, and 8.3±21.7 on post-ESD days 1, 2, 3, and 4, respectively (Fig. 3A). For the 6 patients of the hyperacidic group (tentative classification), omeprazole significantly ($p<0.001$) decreased the mean %time pH<4 (from 93.8±5.6 on pre-ESD day 1 to 66.0±30.4, 36.8±28.8, 24.6±31.2, and 21.1±31.6 on post-ESD days 1, 2, 3, and 4, respectively), although the intragastric pH after omeprazole administration remained <4 for two-thirds of the time on post-ESD day 1. The mean %time pH<4 of the patients of the mesoacidic group changed from 43.8±16.3 on pre-ESD day 1 to 4.5±3.5, 2.7±4.7, 16.7±34.7, and 0.3±0.4 on post-ESD days 1, 2, 3, and 4, respectively, and the corresponding values of patients of the hypoacidic group changed from 3.25±7.96 on pre-ESD day 1 to 0±0, 0.08±0.2, 0±0, and 0±0 on post-ESD days 1, 2, 3, and 4, respectively (Fig. 3B).

4. Correlation between median 24-hour pH and fixed-time pH, and the prediction of omeprazole acid-inhibiting efficacy with the value of fixed-time pH

The intragastric pH at 9 am ranged from 1.0 to 7.8 in these 20 patients with gastric cancer, and the mean±SD was 4.8±2.41. The correlation between the 9 am pH and the median 24-hour pH on pre-ESD day 1 was considered extremely significant ($p<0.0001$, correlation coefficient=0.9058 ; Fig. 4).

We next analyzed the relationship between the

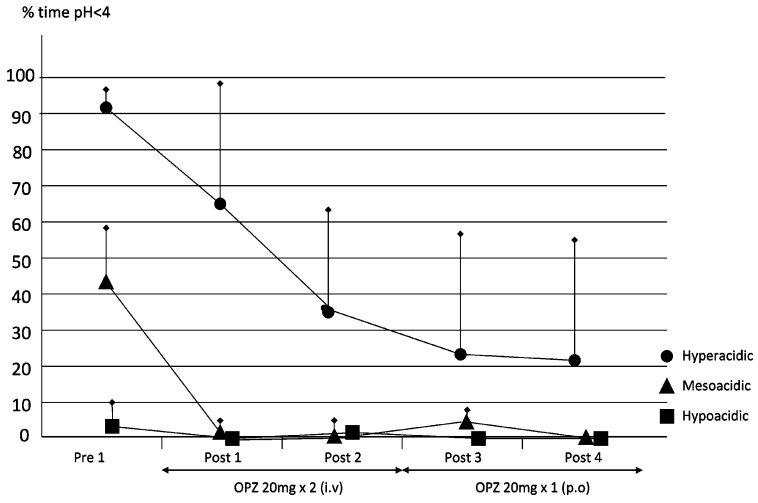


Fig. 3B. Comparison of mean %time pH<4 among the 3 groups—hyperacidic, mesoacidic, and hypoacidic—which were defined as having a mean %time pH<4 of =80%, 20% to 80%, and =20%, respectively. For the 5 patients of the hyperacidic group, omeprazole significantly ($p<0.001$) decreased the mean %time pH< 4, although the intragastric pH after omeprazole administration remained<4 for two-thirds of the time on post-ESD day 1.

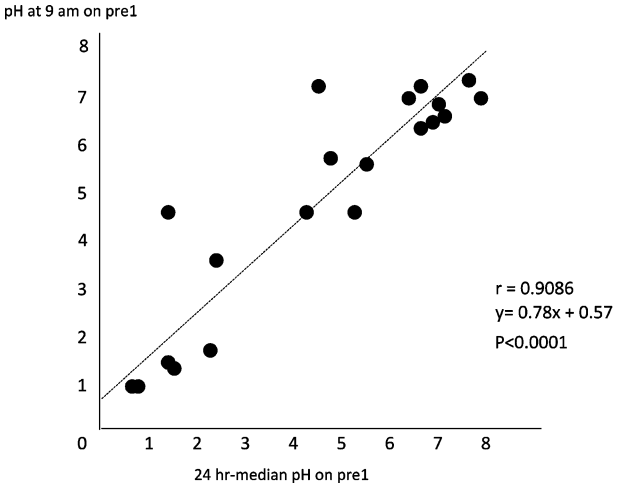


Fig. 4. The correlation between the fixed-point pH observation at 9 am and the mean 24-hour pH on pre-ESD day 1 was considered extremely significant.

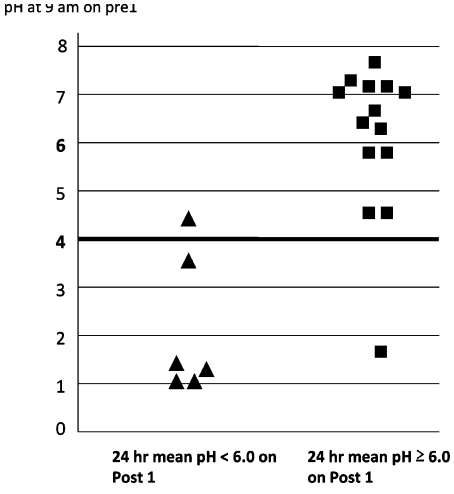


Fig. 5. Fixed-point observation of intragastric pH environments and mean 24-hour pH on post-ESD day 1.

values of 9 am pH and the efficacy of acid suppression with omeprazole. In 5 of 6 patients in whom the mean 24-hour pH on post-ESD day 1 was lower than 6 despite treatment with omeprazole, basal pH values at 9 am were <4. In contrast, the pH was >4 in 13 of 14 patients in whom the mean 24-hour pH on post-ESD day 1 was =6 during treatment with omeprazole (Fig. 5).

Discussion

We evaluated the intragastric acid environment with a telemetric catheter-free system, which was developed to monitor esophageal pH without the inconvenience of a nasopharyngeal electrode[8]. To date, 2 studies have reported that this pH monitoring system in practical for assessing intragastric pH[17,18]. However, the intragastric sites to which the pH capsule could be attached were limited in these previous

studies because the original delivery system, which was designed for esophageal attachment, was used. In the present study, we successfully placed the pH capsule on the desired target region in the stomach and monitored intragastric pH with the method described herein. The gastric cardia, fundus, corpus, and antrum show different pH values in a gradient from hyperacidic to hypoacidic[16,19]. If a single site is chosen to monitor intragastric pH as a measure of gastric acid secretion, the site should be in the oxyntic area, in which the parietal cells secrete acid. Thus, we chose the greater curvature of the upper corpus as the target site for pH monitoring. A noteworthy limitation of our study is that we assessed the intragastric acid environment at only 1 site. Because intragastric pH can be monitored at multiple sites with this method, studies with multiple monitoring by means of the telemetric catheter-free system will enhance our understanding of the intragastric acid environment.

Gastric cancers, with the exception of gastroesophageal junction adenocarcinoma, occur in the gastric mucosa with glandular atrophy or intestinal metaplasia or both, whereby the acid secretory function of the oxyntic gland is profoundly impaired. Patients with distal gastric carcinomas have levels of acid secretion much lower than those in controls subjects without cancer or in patients with adenocarcinomas of the gastroesophageal junction[20]. Nevertheless, acid suppressants are administered to prevent hemorrhage from ESD-induced ulcers in patients with distal gastric carcinoma[7], which are the majority of neoplasias for which ESD is indicated. To establish the rationale for acid suppression to prevent gastric hemorrhage from ESD-induced ulcers, we examined the intragastric acid status and its alteration by a PPI in patients with gastric cancer. Our data demonstrate that acid suppression is not required in one-third of patients with early gastric cancer, as these patients showed a mean 24-hour gastric pH$>$6 at baseline. The remaining two-thirds of patients with early gastric cancer may need acid suppression to prevent hemorrhage from ESD-induced ulcers.

Blood clot stability and gastric mucosal bleeding are extremely sensitive to intragastric pH levels. Acid impairs clot formation by inhibiting platelet aggregation and causing platelet disaggregation. A pH of at least 6 is required to significantly reverse this effect, according to the results of *in vitro*[12,13] and animal studies[14]. Acid also accelerates clot lysis through a predominantly acid-stimulated pepsin mechanism, whereas acid suppression may favor antifibrinolysis. *In vivo* animal studies indicate that gastric mucosal bleeding time decreases significantly at pH$=$6.4. For patients with bleeding peptic ulcers in whom initial hemostasis has been achieved with endoscopic therapy, the rebleeding rate was higher for those patients with a mean intragastric pH$<$6[15]. Therefore, the goal of acid suppression to prevent gastric hemorrhage may be to maintain an intragastric pH$=$6. In 60% of patients with gastric cancer and a basal intragastric pH$<$6, low-dosage omeprazole effectively increased the intragastric pH to $>$6 from post-ESD days 1 to 4. However, omeprazole treatment did not achieve the target for acid suppression in the remaining patients, who represented 30% of the tested patients with gastric cancer.

Complete acid suppression may be necessary to maintain an intragastric pH level$=$6. If the fasting volume of the intragastric fluid with pH 7 is 50 ml, only 3 μL of the parietal cell secretion is theoretically required to decrease the pH from 7 to 5[21]. Therefore, essentially every parietal cell must be inhibited continuously to maintain an intragastric pH level$=$6, which is the target pH for preventing gastric hemorrhage. Previous studies have demonstrated that intermittent bolus and oral administration of omeprazole fails to reliably maintain an intragastric pH$=$6 in patients with bleeding peptic ulcers[21]. The goal of acid suppression could only be achieved with bolus administration of omeprazole (e.g., 80 mg), followed by constant infusion (e.g., 8 mg/hour)[22,23]. The rationale for patients with peptic ulcer appears valid for 30% of patients with early gastric cancer, and attempts at acid suppression with low doses of omeprazole are particularly ineffective in patients with gastric cancer and the extensive metabolizer genotype of CYP2C19. Because the bolus dosage of omeprazole permitted by the Japanese health insurance system is 20 mg twice a day and because continuous infusion is not approved,

we performed the present study with a low dose of omeprazole. Although the present study included no cases of bleeding ulcer, a high dose of a PPI or a high dose followed by constant infusion should be examined for efficacy in preventing hemorrhage from ESD-induced gastric ulcers in patients with gastric cancer who undergo ESD.

Although the Bravo wireless pH capsule is simply attached to the gastric wall and can be used for long-term monitoring of intragastric pH, the system is not easy to use, and the data obtained with the system are not readily applicable to daily clinical use. We have shown that values of intragastric pH at 9 am are well correlated with mean 24-hour pH at baseline and might be used to predict the efficacy of acid suppression with omeprazole. As a part of daily treatment, omeprazole administered at low doses might sufficiently inhibit gastric acidity in patients with gastric neoplasia if intragastric pH measured at the beginning of ESD is >4, and a higher dose of omeprazole may be necessary if the pH is <4.

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