ORIGINAL ARTICLE

TJG
The Turkish Journal of Gastroenterology

Effective administration method of intravenous proton pump inhibitor: A novel testing using a BRAVO catheterless pH monitoring system

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Background/aims: *This study investigated the use of the BRAVO catheterless pH monitoring system to determine the effective administration method of intravenous proton pump inhibitor and the effectiveness of 80 mg pantoprazole per day on the regulation of gastric acid.* ***Methods:*** *A total of 32 patients who underwent endoscopic resection were randomly assigned to the repeated bolus injections group (40 mg dose, twice per day) and continuous infusion group (mixed with 5% glucose, continuous infusion of 80 mg per day). Then, pantoprazole was administered and intragastric pH was measured for 48 hours through a BRAVO capsule. The length of time until the intragastric pH reached 4 and 6 after administration was measured, as well as the mean/median pH for 48 hours and the fraction times (%) of pH >4 and >6 for 48 hours. The factors affecting intragastric pH were also analyzed.* ***Results:*** *There were no complications due to the attachment of the BRAVO capsule. No significant differences according to administration methods were found in all factors. Only Helicobacter pylori had significant effect on the fraction times (%) of pH >4 and >6 for 48 hours ($p<0.05$).* ***Conclusions:*** *The effects of intravenous proton pump inhibitor were similar between the administration methods. Therefore, the repeated bolus injection method, which is relatively simple, is a good choice. Regarding the dose of intravenous pantoprazole, which is used after successful endoscopic hemostasis, 80 mg would be sufficient. We hope that this study encourages the use of the BRAVO catheterless pH monitoring system.*

Key words: BRAVO catheterless pH monitoring system, proton pump inhibitor, intravenous, repeated bolus injections, continuous infusion

Proton pompa inhibitörünün intravenöz olarak etkin kullanılması: BRAVO katetersiz pH takip sistemi kullanılarak test edilmesi

Amaç: *Bu çalışmanın amacı, proton pompa inhibitörünün intravenöz verilmesinin etkinliğinin değerlendirilmesinde, BRAVO katetersiz pH takip sisteminin kullanılarak, günde 80 mg pantoprazolun gastrik asit düzenlenmesindeki etkinliğinin değerlendirilmesidir.* ***Yöntem:*** *Endoskopik rezeksiyon geçiren 32 hasta rastgele tekrarlayan bolus enjeksiyon grubu (40 mg günde iki kez) ve devamlı infüzyon grubuna (% 5 dekstroz içerisinde 80 mg devamlı infüzyon) ayrıldı. Ardından pantoprazol verilerek intragastrik pH 48 saat boyunca BRAVO kapsül ile ölçüldü. İntragastrik pH'nın tedavi ile 4 ve 6'ya ulaşma süreleri ölçüldü, ayrıca ortalama/ortanca 48 saatlik pH ve pH'nın 4 ve 6'nın üzerinde seyrettiği süre fraksiyonları (%) ölçüldü. İntragastrik pH'ya etki eden faktörler de analiz edildi.* ***Bulgular:*** *BRAVO kapsül yerleştirilmesine bağlı hiç komplikasyon görülmedi. Bütün faktörler açısından ilacın verilme şekliyle ilişkili farklılık saptanmadı. pH'nın 48 saat boyunca >4 ve >6 olduğu zaman fraksiyonlarına (%) anlamlı etkisi olan tek faktör, Helicobacter pylori idi ($p<0.05$).* ***Sonuç:*** *İntravenöz proton pompa inhibitörü uygulama şekillerine göre etkinlik açısından fark bulunmamaktadır. Bu nedenle, nispeten daha kolay olan tekrarlayan bolus enjeksiyonlar iyi bir tercihtir. Başarılı endoskopik hemostazdan sonra kullanılan intravenöz pantoprazolün dozu açısından, 80 mg yeterlidir. Umuyoruz ki, bu çalışma BRAVO katetersiz pH takip sisteminin kulanılmasını özendirecektir.*

Anahtar kelimeler: BRAVO katetersiz pH takip sistemi, proton pompa inhibitörü, intravenöz, tekrarlayan bolus enjeksiyonlar, devamlı infüzyon

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Manuscript received: 31.10.2010 **Accepted:** 23.12.2010

Turk J Gastroenterol 2011; 22 (6): 575-581
doi: 10.4318/tjg.2011.0253

INTRODUCTION

The use of proton pump inhibitor (PPI) on patients with peptic ulcer bleeding is effective in the prevention of rebleeding (1-4). Rebleeding occurs after successful endoscopic hemostasis within a few days in most cases. For a quick and continuous regulation of gastric acid, intensive regimen (80 mg bolus followed by 8 mg/hour (h) as continuous infusion of pantoprazole for 72 h) after loading of intravenous (IV) PPI is recommended (1,4). Two methods of IV administration of PPI are continuous infusion (5) and repeated bolus injections (6). Considering the short half-life and tubulovesicle membrane recycling, continuous infusion is thought to be advantageous for pH regulation. However, there is still debate on the administration method, and studies that directly compare them are rare (7).

Even though *in vitro* research found that intragastric pH >6 is ideal (8) and that 8 mg/h after loading 80 mg is required to maintain intragastric pH of >6 (7,9), clinical application of high-dose IV injection is difficult because it results in a financial burden for patients. Under the circumstance where endoscopic hemostasis has already been achieved, the key to the prevention of rebleeding is to stabilize the blood clots that have formed. Thus, it is more realistic to maintain a pH of at least 4, which is the minimum value at which pepsin is not activated (10). Another view is that East Asian patients, particularly Koreans, unlike Western patients, have relatively fewer parietal cells (11), a higher prevalence of *Helicobacter pylori (H. pylori)* (12), and higher frequency of poor metabolizer (hereinafter called PM) of PPI (13,14); therefore, pH regulation is effective even with smaller volumes. However, low-dose IV PPI (40 mg/day, pantoprazole) in Korean patients failed to sufficiently increase pH (15).

Therefore, the authors conducted a prospective randomized clinical study using the BRAVO catheterless pH monitoring system, which is mainly used on the esophagus, investigated the effective administration method of IV PPI, and determined whether 80 mg per day of pantoprazole is an appropriate dose for regulation of gastric acid.

MATERIALS AND METHODS

Subjects of Study

A prospective study was conducted on patients who underwent endoscopic resection for gastric neoplasm at Kosin University Gospel Hospital between April and September 2008. The study plan was approved by the Kosin Foundation Institutional Review Board, and we explained the purpose of this study to all the subjects before treatment. Written consent was obtained from each of them. Patients who were taking PPI or H2-receptor antagonists, had hepatic dysfunction (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >120 U/L) or renal dysfunction (creatinine >2.0 mg/dl), had a history of gastric surgery, had a pacemaker or implantable cardiac defibrillator (ICD), had a severe bleeding tendency, experienced severe complications during the endoscopic resection, did not consent to the examinations, or underwent endoscopic resection on their gastric upper body, and pregnant women were excluded.

For the sample size, SD (standard deviation) 10%, α=0.05, and β=0.2 were given based on a prior study (16). Thus, the sample size was determined as 17 per group, and a total of 38 subjects were enrolled in consideration of a 10% elimination rate. Among the 38 subjects, 32 were finally included in the study, excluding two subjects who did not follow the protocol and four subjects whose BRAVO capsules dislodged spontaneously. Of these 32 subjects, 14 who underwent the procedures on even days were randomly assigned to the continuous infusion group and 18 subjects who underwent the procedure on odd days were randomly assigned to the repeated bolus injections group. The study design flow chart is shown in Figure 1.

Methods

H. pylori Infection Rate

All the subjects underwent tests of serum *H. pylori* antibodies, urea breath test (UBT), and rapid urease test. Those who tested positive on at least two occasions were defined as the *H. pylori*-infec-

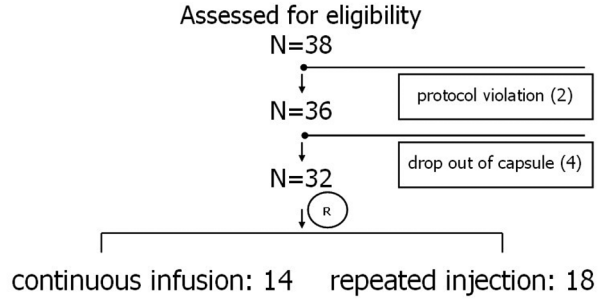

Figure 1. Flow chart of patients enrolled in the final analysis.

ted group and those who were negative for at least two tests were defined as the non-infected group.

CYP2C19 Genotyping

DNA was extracted from whole blood using an AccuPrep Genomic DNA extraction kit (Bioneer Co.). The isolated DNA (100 ng) was added to a polymerase chain reaction (PCR) tube, and template (20-30 ng/ul), CYP2C19 PM-wild (or CYP2C19-mutant) and 8-Mop solution were mixed. The multiplex master mix was added to amplify the entire CYP2C19 gene. PCR was carried out using Applied Biosystems (Foster City, CA). The tube was placed in a 94°C thermal cycler for 5 minutes (min), followed by 35 cycles of 94°C for 30 seconds (sec), 63°C for 30 sec, and 72°C for 45 sec. The final extension was performed at 72°C for 10 minutes (min). Thereafter, 5 ul of the PCR products and CYP2C19 marker were applied on a 2% agarose gel containing ethidium bromide for electrophoresis.

Placement of the Bravo°,R capsule

The capsule was mounted within 30 min after endoscopic resection. First, the gastroscope was inserted down to the mid-esophagus and the Bravo°,R pH monitoring system (Medtronic, Shoreview, MI, USA) was opened. Then, the delivery unit was mounted with the capsule attached to the scope and pushed down to the gastric upper body through the mouth. The capsule was designed to attach to the greater curvature or posterior wall of the gastric upper body. The delivery unit was closely attached to the gastric body and aspirated to the maximum with the endoscope to remove any residual air from the stomach. After removing the endoscope, the gastric mucosa was sucked through the suction hole connected to the delivery unit at 500 mmHg for 60 sec to the small grooves on the capsule surface. Then, the safety pin was removed from the delivery unit, and the button was pressed (at this time the small pin attached to the capsule pierces the mucosa sucked into the capsule so that the capsule is fixed on the mucosa). After removing the delivery unit, it was confirmed by endoscope again that the capsule was installed properly (Figure 2).

PPI Administration and pH Monitoring

After installation of the Bravo°,R capsule, IV pantoprazole (Pantoline; Dong-A Pharmaceutical, Korea) was administered in accordance with the agreed method. For the continuous infusion group, 40 mg of pantoprazole mixed with 500 ml of 5% glucose was continuously infused for 48 h at the same speed, while the fluid was replaced every 12 h (80 mg in total for 1 day). For the repeated bolus injections group, 40 mg of pantoprazole was repeatedly injected every 12 h. Immediately after the administration of pantoprazole, the Bravo°,R system was switched on to begin pH monitoring, which was done for 48 h. All the patients fasted for 48 h. The researchers who were unaware of the IV administration method read the results. The length of time until the intragastric pH reached 4 and 6, the mean/median pH for 48 h, and the fraction times (%) of pH >4 and >6 for 48 h were analyzed for each administration method. The % time of pH >4 was subdivided into Day 1 and Day 2.

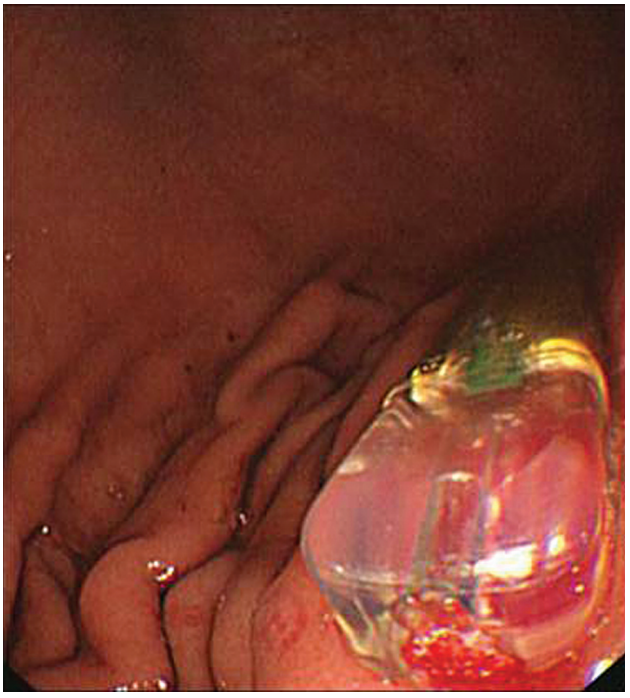

Figure 2. Bravo°,R capsule is installed properly in the greater curvature of the gastric upper body.

Study Endpoints

The effects according to the administration methods (continuous infusion and repeated bolus injections) on the mean/median pH and the fraction times (%) of pH >4 and >6 for 48 h were examined (primary endpoint). The effects of pantoprazole 80 mg and the influencing factors on intragastric pH (secondary endpoint) were also examined.

Statistical Analysis

Data were analyzed using SPSS version 12.0 and SAS version 9.1. All the measurements were indicated by mean±standard deviation. The characte-

ristics of the infusion and injection groups were compared using the Student's t-test and chi-square test. Pearson's correlation coefficient was used to evaluate the relation between intragastric pH and age. The mean comparison of intragastric pH between various patient characteristics was done using Student's t-test and ANOVA. Statistical significance was determined by $p<0.05$.

RESULTS

Characteristics of Subjects

The mean age was 59.5 years. There were no significant differences between the two groups regarding age, sex, smoking history, CYP2C19 genotypes, *H. pylori* prevalence, causative diseases (adenoma, early gastric cancer), and tumor location (Table 1). PM was 21% and *H. pylori* positivity was 66%, which was higher than that of Western studies. There were no complications during the capsule insertion, and the baseline pH was approximately 4.3.

pH Analysis using Bravo°,R Capsule

The lengths of time until pH reached 4 and 6 after PPI administration for 32 subjects were 4.12±6.94 versus 3.70±7.52 (difference, 0.42; 95% CI of difference: -4.88~5.71; p=0.874) and 4.77±7.18 versus 1.83±3.82 (difference, 2.95; 95% CI of difference: -1.40~7.29; p=0.188) for the continuous infusion group (n=14) and the repeated bolus injections group (n=18), respectively. The mean pH and median pH for 48 h were 6.13±1.91 versus 6.54±1.77 (difference, -0.41; 95% CI of difference: -1.74~0.92; p=0.534) and 6.24±2.12 versus 6.63±1.84 (difference, -0.39; 95% CI of difference: -1.82~1.04; p=0.581), respectively. However, they were both high (Figure 3). The % times of pH >4 or pH >6 for 48 h were 70.13±28.44 versus 75.75±23.53 (difference, -2.70; 95% CI of difference: -11.7~6.31; p=0.546) and 62.27±33.81 versus 64.60±35.50 (difference, -1.12; 95% CI of difference: -13.26~11.03; p=0.852). There was no significant difference between the two groups (Table 2). The % times of pH >4 were Day 1 (63.0%, 67.9%) and Day 2 (77.2%, 83.5%), without significant differences.

Influencing Factors on Intragastric pH

The only influencing factor on intragastric pH was *H. pylori*. The baseline pH values for *H. pylori*-negative and -positive patients were 3.22±2.64 and 4.91±2.68, respectively, with no statistically significant difference ($p>0.05$). The mean pH values for 48 h were 5.42±2.28 versus 6.85±1.13 (difference, -1.43; 95% CI of difference: -2.73~-0.14; p=0.075). % times of pH >4 for 48 h were 55.08±31.02 versus 82.83±15.80 (difference, -27.75; 95% CI of difference: -44.53~-10.98; p=0.016), and of pH >6 for 48 h were 45.78±35.85 versus 72.90±30.13 (difference, -27.12; 95% CI of difference: -51.56~-2.69; p=0.031), and they showed significant differences (Table 3).

DISCUSSION

The authors divided 32 subjects into a continuous infusion group (14 subjects) and repeated bolus injections group (18 subjects) to determine the most effective method for IV administration of PPI, and investigated if 80 mg of pantoprazole per day, which is a practical dose often used in clinical situ-

Table 1. Characteristics of the study groups

	Infusion, n=14 (%)	Injection, n=18 (%)	p
Mean (±SE) age	58.64±8.93	60.44±10.10	0.603
Male / Female	9 (64.3)/5 (35.7)	9 (50.0)/9 (50.0)	0.490
Smoking history (Yes/No)	7 (50.0)/7 (50.0)	5 (27.8)/13 (72.2)	0.198
CYP2C19 genotype			0.592
• Homozygous extensive	4 (28.6)	5 (27.8)	
• Heterozygous extensive	8 (57.1)	8 (44.4)	
• Poor metabolizer	2 (14.3)	5 (27.8)	
H. pylori infection			1.000
• Positive	9 (64.3)	12 (66.7)	
• Negative	5 (35.7)	6 (33.3)	
Causative disease			0.267
• Cancer	6 (42.9)	4 (22.2)	
• Adenoma	8 (57.1)	14 (77.8)	
Tumor location			0.183
• Proximal third	0 (0.0)	1 (5.6)	
• Middle third	2 (14.3)	0 (0.0)	
• Distal third	12 (85.7)	17 (94.4)	

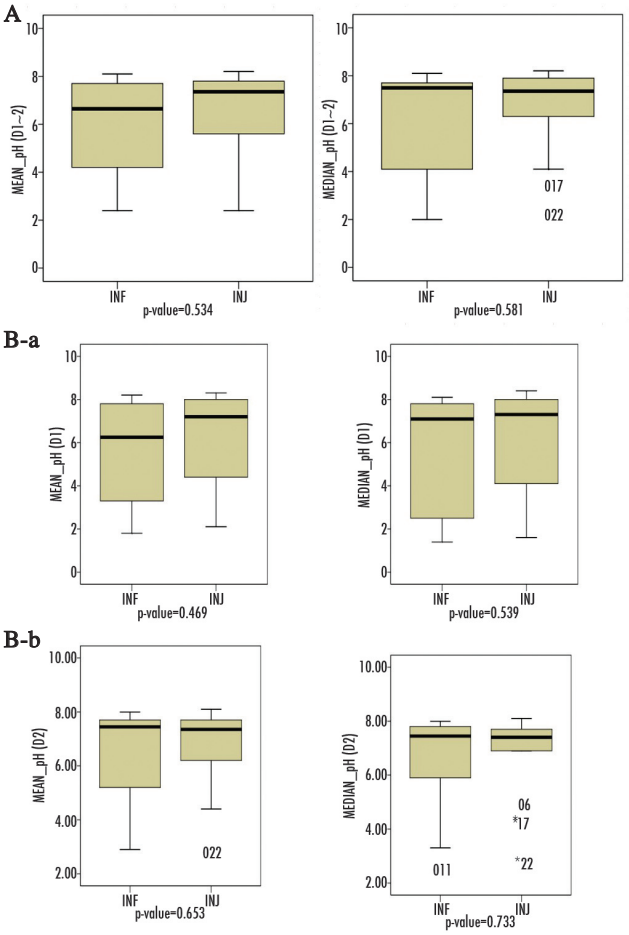

Figure 3. (A) Comparison of the efficacy of infusion (INF) and injection (INJ) of pantoprazole on mean pH (Left) and median pH (Right) during 48 h. (B) Mean pH (Left) and Median pH (Right) on day 1(a) and day 2 (b).

ations, could effectively regulate intragastric pH. The length of time until pH reached 4 and 6 was longer than the results from previous studies because the PPI loading step was omitted. The PPI reached them slightly faster in the repeated bolus injections group as expected, but there was no significant difference between the two groups. Regarding the mean/median pH for 48 h and the % times of pH >4 and >6 for 48 h, no differences were found between the administration methods, and no differences were found within 24 h (Day 1) of their administration. Considering that continuous infusion is cumbersome because it must be mixed with fluid and requires a longer period of administration, and further, the instability of the drug that may be caused by long exposure at room temperature, repeated bolus injection, which is a relatively simple method, seems to be a better choice.

Mean pH (6.13±1.91 versus 6.54±1.77) and median pH (6.24±2.12 versus 6.63±1.84) for 48 h were high in both groups (continuous infusion versus repeated bolus injections), without differences. The reason that 80 mg per day without bolus loading effectively regulated intragastric pH was because the baseline pH values of the subjects were higher than those of the Western studies. It is estimated that this was due to the high percentage of patients who were *H. pylori*-positive (66%), which was a notable characteristic of this study. It is expected that maintaining pH >4 after successful endoscopic hemostasis will effectively prevent rebleeding (10,17). Because the dose of 80 mg is enough for maintaining pH >4 based on the findings from this study, we believe that there is no need to use high doses for prevention of rebleeding.

Baseline pH has individual differences and some had high baseline pH values. For factors influencing pH, only *H. pylori* was significant, which confirms previous reports that *H. pylori*-positive patients have higher suppression effects against gastric secretion (18,19). This study found that there were no differences in baseline pH between *H. pylori*-positive and -negative patients, but the % time of pH >4 and >6 for 48 h showed significant differences after the use of PPI. It is expected that *H. pylori*-positive patients would have a more severe degree of chronic atrophic gastritis and/or intestinal metaplasia, and the reduction of parietal cell mass caused by these seems to be one reason for these differences. However, this study did not measure the degree of changes in mucosa through

Table 2. Intragastric pH results for 48-hour period of PPI administration

	Infusion (n=14)	Injection (n=18)	Difference (95% CI)	p
Time to pH >4	4.12±6.94	1.40±3.38	2.72 (-1.40~6.84)	0.201
Time to pH >6	4.77±7.18	1.83±3.82	2.95 (-1.40~7.29)	0.188
Mean pH	6.13±1.91	6.54±1.77	-0.41 (-1.74~0.92)	0.534
Median pH	6.24±2.12	6.63±1.84	-0.39 (-1.82~1.04)	0.581
% time of >4	70.13±28.44	75.75±23.53	-2.70 (-11.7~6.31)	0.546
% time of >6	62.27±33.81	64.60±35.50	-1.12 (-13.26~11.03)	0.852

Table 3. Factors influencing 48-h intragastric pH: mean and % time with pH >4 and >6

Group		Mean pH D1~2	Time, pH>4 D1~2 (% time)	Time, pH>6 D1~2 (% time)
Age	r	0.139	0.091	-0.007
	p-value	0.449	0.622	0.972
Sex	Female	5.97±1.99	69.09±29.59	56.87±38.27
	Male	6.66±1.65	76.56±22.17	68.80±30.84
	p-value	0.293	0.4204	0.3363
Smoking	None	6.45±1.80	74.41±25.18	64.88±33.20
	Yes	6.22±1.91	71.42±27.08	61.41±37.29
	p-value	0.736	0.754	0.787
Alcohol	None	6.36±1.55	76.43±20.26	64.04±33.04
	Yes	6.36±2.26	68.06±32.82	62.82±37.63
	p-value	0.998	0.377	0.924
CYP2C19	HomEM	6.08±1.86	70.05±27.57	57.73±35.40
	HetEM	6.81±1.71	77.76±22.82	70.13±32.17
	PM	5.69±1.96	67.24±30.59	56.13±39.56
	p-value	0.347	0.613	0.570
H. pylori	Negative	5.42±2.28	55.08±31.02	45.78±35.85
	Positive	6.85±1.33	82.83±15.80	72.90±30.13
	p-value	0.075	0.016*	0.031*
ABO	A	6.02±2.17	66.61±30.72	58.35±36.92
	B	7.32±0.51	89.26±10.18	85.38±12.33
	AB	6.10±2.83	63.91±17.01	37.95±53.67
	O	5.77±1.96	65.81±26.92	51.44±36.66
	p-value	0.246	0.122	0.079

* p<0.05 Hom EM: Homozygous extensive PM: Poor metabolizer
r: Coefficient of correlation. Het EM: Heterozygous extensive

endoscopic biopsy, which requires examination in the future.

Contrary to our expectations, there was no difference in pH according to CYP2C19 genotyping, which confirms previous reports that significant differences are only found at 40 mg per day (20). Our study reaffirmed that these differences are not found at 80 mg.

This study used the BRAVO system for pH analysis. This system is a newly introduced pH test method for the esophagus. Compared with the conventional catheter method, it offers many benefits as it is more convenient for the patient, and stable pH measurement for 24 h or longer (up to 96 h) is available without any limitations to daily activities for the patient, such as in dining and exercise (21,22). A recent study that compares the BRAVO capsule system with the conventional catheter system found that the former enabled more stable and accurate pH monitoring (23). This study preferred the hemoclip technique as a method of BRAVO capsule attachment as it offers a low early drop rate (20%) (23). In our study, however, we directly attached the capsule to the gastric mucosa through a delivery unit, and 4 subjects (10.5%) had dropped in the early stage. Therefore, if we also consider the convenience of attachment, direct attachment using a delivery unit will be beneficial. This study reconfirmed that the BRAVO system is a useful tool for capsule attachment and pH analysis, which does not exhibit serious complications or errors. It is expected that the use of the BRAVO system for intragastric pH test will gradually increase in the future.

In conclusion, because there were no benefits obtained from administration methods, the relatively simple technique of repeated bolus injections is the recommended choice, and 80 mg seems to be a sufficient dose for IV pantoprazole after successful endoscopic hemostasis.

Acknowledgement: *The study was approved by the Kosin Foundation Institutional Review Board and supported by a grant from Kosin University College of Medicine (2009). Furthermore, we would like to thank all the staff members of the Dong-A Pharmaceutical Co., Korea.*

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