

Proton Pump Inhibitor Use before Percutaneous Endoscopic Gastrostomy Is Associated with Adverse Outcomes

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Background/Aims: Knowledge of the risk factors associated with adverse outcomes after percutaneous endoscopic gastrostomy (PEG) may be helpful for developing PEG recommendations. The purpose of this study was to identify the clinical risk factors associated with adverse clinical outcomes after PEG, especially regarding the use of proton pump inhibitors (PPIs). **Methods:** We retrospectively reviewed the data from PEG patients at seven university hospitals between June 2006 and January 2012. All patients were followed up through February 2012 after PEG, and the clinical risk factors for adverse clinical outcomes after PEG were analyzed. **Results:** Data from 1,021 PEG patients were analyzed. PPI users were more frequently included in the complication group than the noncomplication group ($p=0.040$). PEG-related complications ($p=0.040$) and mortality ($p=0.003$) were more frequent in the PPI group than in the control group. In the subgroup analysis of complicated PEG cases, infectious complications were more frequently found in the PPI group than in the control group (35.8% vs 27.8%). After adjustment for multiple possible confounding factors, PPI users (odds ratio, 1.531; 95% confidence interval, 1.017 to 2.305) and diabetic patients had increased mortality after PEG. **Conclusions:** PPI use may be associated with adverse outcomes in patients with PEG; however, further prospective studies investigating this issue are warranted. (*Gut Liver* 2014;8:248-253)

Key Words: Percutaneous endoscopic gastrostomy; Proton pump inhibitors; Mortality; Complication; Risk factors

INTRODUCTION

Percutaneous endoscopic gastrostomy (PEG) is an established procedure for providing nutrients through the intestine.^{1,2} Although PEG is simple to perform, it has a general complication rate of up to 50% and major complications occur in up to 7% of cases.³⁻⁶ Common complications reported after PEG include wound infection, aspiration pneumonia, peritonitis, or bleeding.^{3,4} Knowledge about the risk factors associated with adverse clinical outcomes after PEG may be helpful for the selection and recommendation of PEG.

Previously studied risk factors associated with a high mortality and complication rate after PEG include low serum albumin levels, high C-reactive protein (CRP) levels, advanced patient age, low body mass index (BMI), and comorbidities.⁷⁻¹⁷ However, little is known about whether the proton pump inhibitor (PPI) use may be associated with the adverse outcomes of PEG. PPI use may potentially increase the susceptibility to infection and pneumonia,¹⁸⁻²⁴ which are common complications of PEG. Furthermore, PPI user in PEG patients may be associated with the higher rate of cardiovascular and cerebrovascular comorbidities.²⁵ Therefore, it is hypothesized that PPI use in PEG patients might be associated with the adverse outcomes of PEG.

The purpose of this study was to identify the clinical predic-

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tors of adverse outcomes of PEG, especially focused on PPI use. To the best of our knowledge, this study is the first study to evaluate the association of PPI use with adverse outcomes of PEG.

MATERIALS AND METHODS

1. Patients

This study analyzed the clinical outcomes of PEG among all consecutive patients who underwent PEG at seven university hospitals in the Republic of Korea between June 2006 and January 2012. Patients with the following conditions were excluded: 1) an age of <18 years, 2) a personal history of gastrectomy, or 3) insufficient data. Simple PEG changes during the study period after an initial PEG placement were also excluded. Data were collected on patient age, gender, weight, height, BMI, diabetes mellitus (DM), indications for PEG (neurological disease, stroke, malignancy, hypoxic brain damage, or others), current medications (PPIs, H₂ receptor antagonists [H₂RAs], antacids, antiplatelet agents, anticoagulants, nonsteroidal anti-inflammatory drugs, and immunosuppressive agents), laboratory data (white blood cell [WBC], albumin, creatinine, and CRP) within 72 hours before PEG, complications, mortality, and duration of hospitalization after PEG. The incidence of complications and mortality of PEG were compared over the study period between a PPI group and a control group. All patients were followed up to February 2012 for complications and mortality occurred after PEG. This study was performed according to the principles of the Declaration of Helsinki, and was approved by the Institutional Review Board of each hospital.

2. Definitions

The PPI user was defined as patients who were taking standard dose of PPIs at least 48 hours before PEG placement, and all PPIs were included in the PPI group because all PPIs are similar in efficacy and potency and generally cause the hypochlorhydria at their therapeutic doses.¹⁸ As most PPIs provide hypochlorhydria from the first day of therapy,¹⁸ PPI use more than 48 hours was defined as a PPI user in this study. In contrast, the control group was defined as patients who had no use of PPI as well as no use of H₂RA or antacid, which can affect the acidity of stomach. DM was defined as a fasting glucose of ≥ 126 mg/dL or use of insulin or hypoglycemic agents.

PEG-related complications included all cases of PEG-related mortality, bowel perforation, post-PEG gastrointestinal bleeding, peritonitis, fever, pneumonia, peristomal leaks, or infection. PEG-related infectious complications included all cases of peristomal infection, peritonitis, and pneumonia. However, repeat procedure or second puncture at the time of PEG or asymptomatic pneumoperitoneum was not considered as a complication in this study.

3. Percutaneous endoscopic gastrostomy

PEG was performed only if the patient's physicians estimated that the patient would otherwise need a nasogastric tube feeding for more than 30 days. Patients with a current diagnosis of sepsis, ascites, coagulation disorders, or severely compromised cardiopulmonary function were excluded from indications of PEG. Most of the patients had been fed by nasogastric tube before the PEG insertion procedure. The PEG procedure was performed by either attending gastroenterologists or by experienced fellows under direct supervision of the attending gastroenterologists. The signs and symptoms of the potential complications of PEG were explained to the patients and/or their representatives before starting PEG, and written consent was obtained before the procedure. PEGs were performed with standard upper endoscopes under Ponsky-Gauderer (pull-string) technique in all study hospitals during admission.²⁶ Patients fasted from the midnight before the procedure, and cefazolin 1.0 g was injected intravenously 20 minutes before the procedure. Most of PEGs were performed under conscious sedation by the decision of the performing endoscopists, and midazolam (0.05 to 0.1 mg/kg) or propofol (0.5 to 1 mg/kg) were used for conscious sedation. A 24 F PEG kit (PEG System, Wilson-Cook; Wilson-Cook Medical Inc., Winston-Salem, NC, USA) were used in all study hospitals.

After PEG placement, patients fasted for 12 hours, and began receiving water unless bleeding, ileus, or fever was noted. Caregivers or patients were taught PEG management methods by a regular nurse and/or dietitian of the nutrition support team on how to perform daily care of the PEG tube and wound, solutions to common PEG-related problems, and nutritional advice.

4. Statistical analysis

The primary outcome was the incidence of adverse outcomes after PEG in the PPI group and the control group. Secondary outcomes were the clinical and laboratory characteristics of both groups. Continuous variables were expressed as mean \pm SD, and categorical variables were expressed as numbers (percentage). Comparisons between the two groups were made using either the t-test or Fisher exact test. Tests for proportionality between two groups were made using chi-square tests. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for mortality after PEG. Variables with $p < 0.1$ in the univariate analysis were added to the multivariate logistic regression model to identify independent risk factors associated with mortality after PEG. Statistical significance was defined as $p < 0.05$, and a statistical trend was defined as $p < 0.1$. Statistical analysis was performed using the SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

During the study period, 1,043 patients received PEG at seven

university hospitals. Of these, 22 patients were excluded from data analysis due to insufficient data (n=13) or being <18 years of age (n=9). In total, 1,021 patients were included, with a mean age of 66.1±14 years, and with males (66.7%) being slightly predominated. The median follow-up time was 136 days (range, 1 to 2,693 days).

Table 1 shows the clinical and laboratory characteristics of 1,021 patients who received PEG according to complications. Patients with malignancy were more frequently included in the complication group than noncomplication group (p=0.020). Indications of PEG can't be clarified in 39 cases due to dysphagia or refusal of oral feeding without definite causes in extreme old ages, and these data were excluded from the classification of indication. Patients being treated with PPI, antiplatelet agents or anticoagulants were more frequently included in the complication group than noncomplication group (p=0.040, p=0.016, and p=0.006, respectively). However, two groups were not significantly different in other variables.

Table 1. Clinical and Laboratory Characteristics of 1,021 Percutaneous Endoscopic Gastrostomy Patients with or without Complications

Characteristic	Complication group (n=223)	Non-complication group (n=798)	p-value
Clinical characteristics			
Age, yr	66.8±13.4	65.9±14.6	0.413
Male, gender	149 (66.8)	532 (66.7)	0.967
Body mass index, kg/m ²	20.8±3.6	21.1±3.5	0.363
Diabetes mellitus	60 (26.9)	167 (20.9)	0.054
Indications of PEG*			
Neurological disease	68 (30.5)	233 (29.2)	0.708
Stroke	97 (43.5)	328 (41.1)	0.521
Malignancy	31 (13.9)	69 (8.6)	0.020
Hypoxic brain damage	9 (4.0)	47 (5.9)	0.282
Esophageal fistula	2 (0.9)	17 (2.1)	0.228
Others	13 (5.8)	68 (8.5)	0.189
Current medications			
Proton pump inhibitors	53 (23.8)	150 (18.8)	0.040
Antiplatelet agents	47 (21.1)	115 (14.4)	0.016
Anticoagulants	15 (6.7)	19 (2.4)	0.006
NSAIDs	9 (4.0)	28 (3.5)	0.993
Immunosuppressive agents	13 (5.8)	29 (3.6)	0.144
Laboratory data			
WBC, ×10 ³ cells/μL	6.6±5.6	6.5±4.7	0.820
Albumin, g/dL	3.4±0.6	3.4±0.5	0.644
Creatinine, mg/dL	0.9±0.7	0.9±0.9	0.676
C-reactive protein, mg/dL	6.7±21.8	5.2±13.7	0.254

Data are presented as mean±SD or number (%).

PEG, percutaneous endoscopic gastrostomy; NSAID, nonsteroidal anti-inflammatory drug; WBC, white blood cell.

*Indications of PEG could not be clarified in 39 cases, and these cases were excluded from the classification of indication.

Table 2 shows the clinical and laboratory characteristics of 675 PEG patients according to PPI use: a PPI group (n=203) and a control group (n=472). The remaining 346 patients were excluded from data analysis as they did not satisfy the criteria of a PPI group and a control group, which was described in the Materials and Methods. Two groups were not significantly different in age, gender, BMI, or DM. Patients with neurological disease or stroke were more frequently included in the PPI group (p=0.000, respectively), and patients under antiplatelet agents and anticoagulants were more frequently included in the PPI group than in the control group (p=0.001 and p=0.039). Laboratory findings of WBCs and albumin were significantly lower in the PPI group than in the control group (all p<0.05). Other variables were equally included in both groups. Patients in the PPI group showed a higher rate of PEG-related complications (p=0.040) and mortality (p=0.003) than those in the control group. In subgroup analysis of complicated PEG cases, infectious complications were more frequently detected in the PPI group than in the control group (35.8% vs 27.8%), however, this difference was not statistically significant (p=0.312). Among infectious complications, occurrences of pneumonia were also more frequently detected in the PPI group than in the control group (20.8% vs 13.3%; p=0.243). The cure rate of complications and duration of hospitalization after PEG were not significantly different between two groups, either.

To identify independent risk factors related to mortality after PEG placement, multivariate analysis was performed after adjusting for age, DM, neurological disease, stroke, use of PPIs, antiplatelet agents or anticoagulants, WBC level, albumin level, and CRP level (Table 3). In this analysis, PPI use (OR, 1.712; 95% CI, 1.147 to 2.555; p=0.009) as well as the presence of DM (OR, 1.853; 95% CI, 1.210 to 2.837; p=0.005) were found to be independent risk factors for increased mortality after PEG placement.

DISCUSSION

To our knowledge, this is the first study examining the association between PPI use and adverse clinical outcomes of PEG. In this study, patients being treated with PPI were more frequently included in the complication group than noncomplication group (p=0.040). PPI users before PEG placement more frequently experienced PEG-related complications (p=0.040) and overall mortality (p=0.003) than those in the control group. Although the difference did not reach statistical significance, infectious complications, and pneumonia were more frequently detected in the PPI group than in the control group (35.8% vs 27.8%, p=0.312 and 20.8% vs 13.3%, p=0.243, respectively) in subgroup analysis of PEG cases with complications. Furthermore, the data indicated that PPI user (OR, 1.531; 95% CI, 1.017 to 2.305) as well as diabetic patients were associated with an increased mortality of PEG, even after adjusting for multiple

Table 2. Comparative Analysis of the Clinical Characteristics and Outcomes of 675 Percutaneous Endoscopic Gastrostomy Patients between the Proton Pump Inhibitor Group versus the Control Group

Characteristic	PPI group (n=203)	Control group (n=472)	p-value
Clinical characteristics			
Age, yr	67.6±14.7	65.5±14.1	0.078
Male, gender	141 (69.5)	313 (66.3)	0.633
Body mass index, kg/m ²	21.4±3.3	21.0±3.6	0.189
Diabetes mellitus	60 (30.0)	97 (20.1)	0.092
Indications of PEG			
Neurological disease	40 (19.7)	166 (35.2)	0.000
Stroke	103 (50.7)	163 (34.5)	0.000
Malignancy	16 (7.9)	54 (11.4)	0.164
Hypoxic brain damage	10 (4.9)	26 (5.5)	0.757
Others	34 (16.7)	63 (13.3)	0.248
Current medications			
Antiplatelet agents	47 (23.2)	62 (13.1)	0.001
Anticoagulants	10 (4.9)	16 (3.4)	0.039
NSAIDs	7 (3.4)	13 (2.8)	0.239
Immunosuppressive agents	12 (5.9)	16 (3.4)	0.132
Laboratory data			
WBC, ×10 ³ cells/μL	6.1±4.8	7.0±5.2	0.042
Albumin, g/dL	3.3±0.5	3.4±0.6	0.001
Creatinine, mg/dL	1.1±1.0	1.0±0.9	0.178
C-reactive protein, mg/dL	7.4±19.7	4.5±12.6	0.056
Outcome data			
PEG-related complications	53 (26.1)	90 (19.1)	0.040
Infectious complications*	19 (35.8)	25 (27.8)	0.312
Noninfectious complications	34 (64.2)	65 (72.2)	
Cure of complications	51 (25.1)	87 (18.4)	0.672
Hospitalization after PEG, day	2.01 (0.2)	2.10 (0.3)	0.726
Death after PEG	80 (39.4)	132 (28.0)	0.003

Data are presented as mean±SD or number (%).

PEG, percutaneous endoscopic gastrostomy; NSAID, nonsteroidal anti-inflammatory drug; WBC, white blood cell.

*PEG-related infectious complications included all cases of peristomal infection, peritonitis, and pneumonia.

possible confounding factors with multivariate analysis.

Most previous studies on outcomes of PEG suggested low albumin levels, high CRP levels, advanced patient age, low BMI, dementia, and comorbidities as potential risk factors for high mortality and complication rates of PEG.⁷⁻¹⁷ Lang *et al.*⁷ reported that the presence of DM, chronic obstructive pulmonary disease, and a low serum albumin level each increased the early mortality risk among PEG patients. In accordance with this report, we also found that the presence of DM was associated with an increased mortality after PEG. However, it is interesting that PPI use before PEG placement was associated with adverse outcomes after PEG procedure, which is a novel finding of this study.

Table 3. Multivariate Analysis of the Associated Variables for Mortality after Percutaneous Endoscopic Gastrostomy Placement

Parameter	OR (95% CI)	p-value
Age, yr (continuous)	1.001 (0.997-1.025)	0.135
Diabetes mellitus (no vs yes)	1.853 (1.210-2.837)	0.005
Neurological disease (no vs yes)	0.684 (0.418-1.122)	0.132
Stroke (no vs yes)	1.509 (0.967-2.356)	0.070
Antiplatelet agents (no vs yes)	0.945 (0.577-1.548)	0.822
Anticoagulants (no vs yes)	0.818 (0.336-1.993)	0.658
PPI use (no vs yes)	1.712 (1.147-2.555)	0.009
WBC, ×10 ³ cells/μL (<11.0 vs ≥11.0)	0.653 (0.310-1.022)	0.059
Albumin, g/dL (≥3.0 vs <3.0)	1.410 (0.893-2.228)	0.141
CRP, mg/dL (<1.0 vs ≥1.0)	1.410 (0.781-2.545)	0.254

OR, odds ratio; CI, confidence interval; PPI, proton pump inhibitor; WBC, white blood cell; CRP, C-reactive protein.

With the widespread use of PPIs, the possible association of PPI use with adverse outcomes after PEG may be considered. Although little is known about the association between PPI use and adverse outcomes of PEG, there might be several possible explanations for this association. First of all, PPI use may simply be a clinical predictor for severe comorbid patients and not the direct cause of these complications. In our study, stroke was more frequently indicated in a PPI group than a control group, and patients using antiplatelet agents or anticoagulants, which may represent the cardiovascular or cerebrovascular comorbidities, were more frequently included in the PPI group. Therefore, the higher mortality rate of PEG in the PPI group may be associated with the higher rate of cardiovascular or cerebrovascular comorbidities in this group, because PPIs are frequently prescribed in these conditions.²⁵ Secondly, the complications of PEG may be potentially increased by the use of PPI itself. In the literature review, the use of PPIs may inhibit the bactericidal activity of neutrophils,²⁷⁻³¹ increase bacterial translocation³² and encourage growth of gut microflora.³³ As a result, PPI use may increase the susceptibility of infectious complications of PEG, such as wound infection or pneumonia. Ono *et al.*³⁴ demonstrated that the wound infection after PEG is increased by gastric hypochlorhydria. In our study, infectious complications including pneumonia, wound infection, and peritonitis were more frequently detected in the PPI group than in the control group, however, the difference did not reach a statistical significance possibly due to a small sample size of cases with infectious complications. Therefore, further large prospective studies on this issue may be warranted to confirm this association.

Our study has an important clinical implication, as it is the first large study to evaluate the association between PPI use and adverse outcomes of PEG. PPIs are available over the counter in many countries and overused,³⁵ and majority of PPI use had no documented indication for their use.³⁶ Therefore, physicians may consider the proper indications of PPI use before PEG place-

ment based on our findings. The other advantage of our study was that we included multiple possible predictors of adverse outcome of PEG and many clinical data including medication history and laboratory findings, which were obtained from multiple endoscopic centers.

However, our study has some limitations. First of all, the study design was retrospective and we can't answer whether PPI users are prone to adverse clinical outcomes unrelated to PPI use (i.e., PPI is simply a clinical predictor) or PPI use itself has the causal relationship with the adverse clinical outcomes. Retrospective study can't answer the cause and effect relationship, and this limitation is not related to our study but inherent in all retrospective study. However, our study may call attention the possible relationship of PPI use and adverse clinical outcomes in patients with PEG, and may draw further prospective studies on this issue. The causal relationship of PPI use and adverse clinical outcomes in patient with PEG will be more clearly elucidated in the future prospective studies. Secondly, the causes of mortality were not clearly demonstrated in our study because of its retrospective nature and multiple comorbid conditions in our study patients. However, the exact causes of mortality in PEG patients might not be clearly identified, either, even in a prospective data collection as PEG patients often have multiple, chronic, debilitating conditions. Thirdly, 346 patients were excluded from data analysis as they did not fulfill the criteria of either the PPI group or the control group. However, our classification scheme was necessary for a clear division of the state of hypochlorhydria because any use of H2RAs or antacids may affect the acidity of stomach, even though they did not use any PPIs.

In conclusion, the use of PPI may be associated with adverse clinical outcomes in patients with PEG, however, further prospective studies on this issue may be warranted to elucidate this association.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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