

Risk of *Clostridium difficile* Infection with the Use of a Proton Pump Inhibitor for Stress Ulcer Prophylaxis in Critically Ill Patients

Youngouk Ro, Chang Soo Eun, Hyun Soo Kim, Ji Yeoun Kim, Young Jae Byun, Kyo-Sang Yoo, and Dong Soo Han

Department of Internal Medicine, Hanyang University Guri Hospital, Guri, Korea

See editorial on page 493.

Background/Aims: Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are commonly prescribed for stress ulcer prophylaxis (SUP) in critically ill patients. Several studies have suggested that the use of PPIs is a potential risk factor for *Clostridium difficile* infection (CDI). We compared the incidences of CDI in the PPI group and H2RA group for SUP in critically ill patients. **Methods:** From August 2005 to July 2012, the incidences of CDI were retrospectively analyzed in patients who were admitted directly to intensive care units and stayed for more than 3 days. SUP-related CDI was defined as a CDI diagnosed during the SUP period. Patient clinical data were analyzed to identify potential risk factors for SUP-related CDI. **Results:** Of the 1,005 patients enrolled (444 patients received PPI and 561 received H2RA), 38 (3.8%) were diagnosed with SUP-related CDI. The incidence of SUP-related CDI was considerably higher in patients who received PPI than in those who received H2RA (6.7% vs 1.8%). PPI use for SUP (odds ratio [OR], 3.3; confidence interval [CI], 1.5 to 7.1; $p=0.003$) and diabetes mellitus (OR, 2.3; CI, 1.2 to 4.7; $p=0.019$) were independent risk factors for SUP-related CDI. **Conclusions:** PPI therapy is associated with a higher risk of SUP-related CDI than H2RA therapy in critically ill patients. (*Gut Liver* 2016;10:581-586)

Key Words: *Clostridium difficile*; Proton pump inhibitor; Histamine-2 receptor antagonist; Critical care

INTRODUCTION

Clostridium difficile infection (CDI) is the most common cause of hospital-acquired infectious diarrhea and can be an important cause of morbidity and death. CDI can worsen clinical signs at a crucial time in critically ill patients. The development of CDI in critically ill patients is associated with high mortality and excessive lengths of stay in intensive care units (ICUs) and hospitals.^{1,2}

The efficacy of stress ulcer prophylaxis (SUP) in critically ill patients is well established, and gastric acid suppressants are commonly prescribed in ICUs.³ In a French multicenter study, 32% of ICU patients received SUP.⁴ Consequently, upper gastrointestinal (UGI) bleeding from stress-related mucosal injury has declined half over the past two decades.⁵ Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are generally prescribed for this purpose. It is unclear which drug is more effective in preventing UGI bleeding.^{6,7} Nevertheless, the use of PPIs as drug of first choice for SUP has gradually increased from 3% in 1998 to 23% in 2002.⁸

Recent studies have suggest that PPIs are associated with the development of CDI in the community and in hospital.⁹⁻¹¹ A meta-analysis of 42 observational studies involving 313,000 participants demonstrated that PPI treatment was associated with the occurrence and recurrence of CDI, whereas H2RA treatment was less harmful.¹²

Although gastric acid suppressants for SUP in critically ill patients have been widely used, there are few studies to analyze increasing incidence of CDI in these patients.¹³⁻¹⁵ Only a handful of studies have examined the risk of CDI in ICUs and general wards.^{12,16,17} This study was performed retrospectively to examine whether PPIs used for SUP in an ICU are associated with a higher incidence of CDI than H2RAs. We hypothesized that the use of PPIs in critically ill patients is associated with a higher incidence of CDI than the use of H2RAs.

Correspondence to: Chang Soo Eun

Department of Internal Medicine, Hanyang University Guri Hospital, 153 Gyeongchun-ro, Guri 11923, Korea

Tel: +82-31-560-2228, Fax: +82-31-555-2998, E-mail: cseun@hanyang.ac.kr

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MATERIALS AND METHODS

1. Patients and study design

We conducted a retrospective study of patients aged at least 18 years who were admitted directly to an ICU between August 2005 and July 2012 and remained there for more than 3 days. Hanyang University Guri Hospital is an urban, academic facility with 600 licensed beds, and it houses 30 ICU beds without separate medical or surgical units. In order to compare the effects of the SUP agents on the development of CDI, we excluded patients with crossover use of the SUP agents, with no use of SUP agents, and with use of SUP agents for less than 3 days. Of the remaining patients—who received a single type of gastric acid suppressant—those with any of the following were subsequently excluded: (1) prior use of antibiotics within 2 months of admission; (2) prior use of a PPI or H2RA within 1 month of admission; (3) a diagnosis of CDI on admission; and (4) transfer to the ICU from another hospital during treatment (Fig. 1).

The study was approved by the Institutional Review Board of Hanyang University Guri Hospital.

2. Definitions and data collection

SUP was defined if a patient in the ICU received a gastric acid suppressant for at least 3 days. CDI was defined as new onset of two or more unformed bowel movements per day more than 48 hours after admission and if *Clostridium difficile* toxin was confirmed by the Premier[®] toxins A and B enzyme immune assay (Meridian Bioscience Inc., Cincinnati, OH, USA) or stool polymerase chain reaction. If CDI developed during SUP or within 3 days after SUP, we regarded it as a SUP-related CDI.

Patient's demographic and clinical data were collected retrospectively from electronic medical records. All clinical data were collected from admission to 3 days after SUP, which was taken to be the period of gastric acid suppression, or to the time of CDI development. Clinical data included age, sex, body mass

index, diagnosis on admission, comorbid illness (hypertension, coronary artery disease [CAD], diabetes mellitus [DM], chronic respiratory disease, immune suppression, end-stage renal disease [ESRD], malignancy, and cirrhosis), and use of antibiotics and immunosuppressive agents, mechanical ventilation and mortality. Acute physiology and chronic health evaluation (APACHE) II scores were calculated for each patient to evaluate severity of illness on admission based on vital signs, laboratory results and the Glasgow coma scale. Since antibiotic treatment is a well-established risk factor for CDI, we characterized antibiotic treatment in terms of number of antibiotics (none, one, two, and more than two) and history of high risk antibiotic use (cephalosporin, penicillin, vancomycin, fluoroquinolone, and carbapenem).

3. Statistical analysis

Univariate analysis was used to screen for potential risk factors that affect the development of CDI during gastric acid suppression using the chi-square test for categorical variables or Student t-test, depending on the distribution of the variable. We judged that a factor was a potential risk factors when the p-value was <0.05. Logistic regression analysis was used for multivariate analysis, and to estimate odds ratios and their 95% confidence intervals. An overall p-value <0.05 was required for statistical significance. Statistical analyses were performed with SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Baseline characteristics and clinical data at admission

A total of 2,339 patients who were above the age of 18 years, were admitted directly to the ICU, and stayed longer than 3 days were identified during the study period. Of these, 1,087 were excluded because they received no SUP treatment or there was crossover use of gastric acid suppressive agents. Of the remaining 1,252 patients treated for SUP with a single agent for at least 3 days, 247 patients were subsequently excluded; 95 for prior use of gastric acid suppressants, 40 for prior use of antibiotics, 109 for transfer from another hospital and 3 for recurrent CDI (Fig. 1). Finally 1,005 patients were enrolled and their baseline characteristics were shown in Table 1.

The median age of the enrolled patients was 60.8 years. The most frequent diagnosis at admission was cerebral hemorrhage (39.3%), followed by heart problems (18.5%). The mean APACHE II score was 20.2. Mean duration of SUP treatment was 13.2 days. A PPI for SUP was prescribed for 444 patients, while the remaining 561 patients were prescribed an H2RA. Among a total of 1,005 enrolled patients, 834 patients (83.0%) received antibiotics treatment during the SUP period or before the diagnosis of CDI.

The characteristics of PPI group and H2RA group were compared in Table 2. The mean age of the PPI group was signifi-

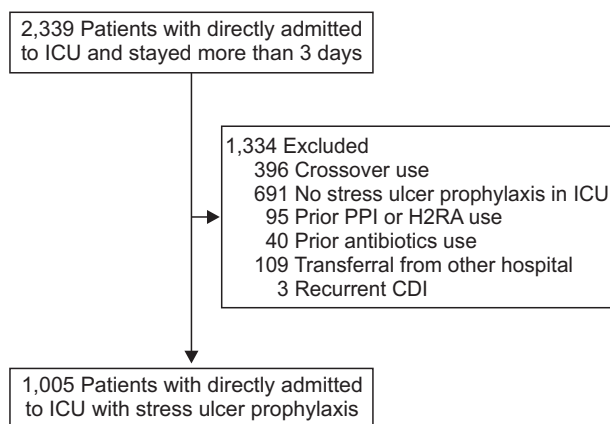


Fig. 1. Flow diagram of the study.

ICU, intensive care units; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonists; CDI, *Clostridium difficile* infection.

Table 1. Baseline Characteristics of Patients

Characteristic	Value
Age, yr	60.8±16.1
Sex	
Male	613 (71.0)
Female	392 (39.0)
APACHE II score	20.2±6.8
Reason of admission	
Heart problem	186 (18.5)
Renal problem	27 (2.7)
Respiratory problem	48 (4.8)
Gastrointestinal problem	81 (8.1)
Intracranial hemorrhage	395 (39.3)
Cerebral infarction	68 (6.8)
Sepsis	41 (4.1)
Others	159 (15.8)
Comorbidity	
Hypertension	437 (43.5)
Coronary artery disease	152 (15.1)
Diabetes mellitus	262 (26.1)
Chronic respiratory disease	55 (5.5)
Heart failure	118 (11.7)
Immune suppression	8 (0.8)
End stage renal disease	58 (5.8)
Malignancy	40 (4.0)
Liver cirrhosis	70 (7.0)
Total days of ICU stay	17.2±28.9
Total days of hospital stay	39.5±60.1
Mortality	271 (27.0)
Stress ulcer prophylaxis	
PPI	444 (44.2)
H2RA	561 (55.8)
Total days of SUP	13.2±13.4
No. of antibiotics	
0	171 (17.0)
1	203 (20.2)
2	390 (38.8)
≥3	241 (24.0)
Types of antibiotics	
Cephalosporin	710 (70.6)
Fluoroquinolone	189 (18.8)
Carbapenem	80 (8.0)
Penicillin	182 (18.1)
Vancomycin	77 (7.7)
Use of steroid (more than 5 day)	385 (38.3)
Mechanical ventilator (more than 48 hr)	470 (46.8)
Diagnosis of CDI during hospital stay	52 (5.2)
Diagnosis of SUP related CDI	38 (3.8)

Data are presented as number (%) or mean±SD. APACHE, acute physiology and chronic health evaluation; ICU, intensive care units; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonists; SUP, stress ulcer prophylaxis; CDI, *Clostridium difficile* infection.

Table 2. Comparison of the PPI Group and H2RA Group

Patient demographics	H2RA group (n=561)	PPI group (n=444)	p-value
Female sex	228 (40.6)	164 (36.9)	0.13
Age, yr	58.7±16.1	63.5±15.7	<0.001
Total days of SUP	11.9±12.8	14.8±13.9	0.001
Total days of ICU stay	21.5±35.8	11.9±14.7	<0.001
Use of antibiotics	491 (87.5)	343 (77.3)	<0.001
No. of antibiotics			0.02
0	70 (12.5)	101 (22.7)	
1	71 (12.7)	132 (29.7)	
2	292 (52.0)	98 (22.1)	
≥3	128 (22.8)	113 (25.5)	
Comorbidity			
Hypertension	250 (44.6)	187 (42.1)	0.24
Coronary artery disease	34 (6.1)	118 (26.6)	<0.001
Diabetes mellitus	108 (19.3)	154 (34.7)	<0.001
Chronic respiratory disease	24 (4.3)	31 (7.0)	0.04
Heart failure	30 (5.3)	88 (19.8)	<0.001
End stage renal disease	11 (2.0)	47 (10.6)	<0.001
Malignancy	19 (3.4)	21 (4.7)	0.18
Liver cirrhosis	6 (1.1)	64 (14.4)	<0.001
Body mass index*	23.1±3.6	22.8±3.6	0.39
Use of steroid (more than 5 day)	350 (62.4)	35 (9.1)	<0.001
Mechanical ventilator (more than 48 hr)	276 (49.2)	194 (43.5)	0.05
APACHE II score	20.6±6.2	19.8±7.5	0.07
Mortality	172 (30.7)	99 (22.3)	0.002

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

PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonists; SUP, stress ulcer prophylaxis; ICU, intensive care units; APACHE, acute physiology and chronic health evaluation.

*These data were calculated from the 698 patients out of a total of 1,005 patients.

cantly higher than that of the H2RA group. The comorbidities (CAD, DM, heart failure, ESRD, and liver cirrhosis) and total days of SUP were significantly higher in the PPI group than in the H2RA group. On the contrary, use of steroid, total days of ICU stay, treatment of mechanical ventilator, and mortality rate were significantly higher in the H2RA group than in the PPI group.

2. Incidence and risk factors for SUP-related CDI

Fifty-two patients (5.2%) were diagnosed as a CDI during their hospital stay and 38 (3.8%) were diagnosed as a CDI during the SUP period. These 38 patients were regarded as a SUP-related CDI. The incidence of SUP-related CDI in the PPI group (6.3%, 28/444) was significantly higher than in the H2RA group (1.8%, 10/561). The clinical characteristics between the "SUP-

Table 3. Comparison of the SUP-Related CDI Group and Non-CDI Group

Patient demographics	SUP-related CDI (n=38)	No CDI (n=953)	p-value
Stress ulcer prophylaxis			
PPI	28 (73.7)	416 (43.7)	<0.001
H2RA	10 (26.3)	527 (55.3)	<0.001
Female sex	16 (42.1)	367 (38.5)	0.74
Age, yr	64.8±14.1	60.7±16.1	0.09
Total days of SUP	15.2±11.9	13.1±13.4	0.35
Total days of ICU stay	28.2±29.2	16.8±28.8	0.02
Use of antibiotics	35 (92.1)	799 (83.8)	0.09
No. of antibiotics			0.02
0	3 (7.9)	154 (16.2)	
1	15 (39.5)	188 (19.7)	
2	10 (26.3)	380 (39.9)	
≥3	10 (26.3)	231 (24.2)	
Types of antibiotics			
Cephalosporin	25 (65.8)	594 (62.3)	0.86
Fluoroquinolone	10 (26.3)	178 (18.7)	0.29
Carbapenem	7 (18.4)	73 (7.7)	0.03
Penicillin	9 (23.7)	170 (17.8)	0.39
Vancomycin	7 (18.4)	69 (7.2)	0.02
Comorbidity			
Hypertension	21 (55.3)	399 (41.9)	0.13
Coronary artery disease	0	152 (15.9)	0.002
Diabetes mellitus	19 (50.0)	238 (25.0)	0.002
Chronic respiratory disease	0	55 (5.8)	0.27
Heart failure	4 (10.5)	113 (11.9)	0.52
Immune suppression	0	8 (0.8)	0.72
End stage renal disease	8 (21.1)	49 (5.1)	0.001
Malignancy	0	40 (4.2)	0.40
Liver cirrhosis	3 (7.9)	67 (7.0)	0.75
Body mass index*	23.4±3.5	22.9±3.6	0.47
Use of steroid (more than 5 day)	9 (23.7)	357 (37.5)	0.09
Mechanical ventilator (more than 48 hr)	22 (57.9)	448 (47.0)	0.19
APACHE II score	21.0±6.7	20.1±6.8	0.90
Mortality	5 (13.2)	261 (27.4)	0.61

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

SUP, stress ulcer prophylaxis; CDI, *Clostridium difficile* infection; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonists; ICU, intensive care units; APACHE, acute physiology and chronic health evaluation.

*These data were calculated from the 698 patients out of a total of 1,005 patients.

Table 4. Risk Factors for Developing SUP-Related CDI in Multivariate Analysis

Variable	OR	95% CI	p-value
Age	1.0	0.9–1.0	0.26
Total days of SUP	1.0	0.9–1.0	0.42
Total days of ICU stay	1.0	0.9–1.1	0.06
PPI for SUP	3.3	1.5–7.1	0.003
Use of antibiotics	2.3	0.9–5.8	0.07
Coronary artery disease	0.0	0.00	0.99
Diabetes mellitus	2.3	1.2–4.7	0.019
Heart failure	0.7	0.2–2.1	0.56
End stage renal disease	2.1	0.8–5.3	0.12
Liver cirrhosis	0.9	0.3–3.0	0.83
Use of steroid	0.5	0.2–1.0	0.06

SUP, stress ulcer prophylaxis; CDI, *Clostridium difficile* infection; OR, odds ratio; CI, confidence interval; ICU, intensive care units; PPI, proton pump inhibitor.

related CDI group” and the “no CDI group” were compared in Table 3. In univariate analysis, PPI use for SUP, number of antibiotics, total days of ICU stay, CAD, DM, and ESRD were significantly associated with the development of CDI during the gastric acid suppression period. Use of carbapenem and vancomycin among the antibiotics were risk factors in univariate analysis. In multivariate analysis, PPI treatment and DM were independent risk factors for SUP-related CDI (Table 4).

In addition, we reviewed the clinical outcomes of SUP-related CDI between the PPI and the H2RA group. Due to the limitation of retrospective study, we were able to analyze 27 patients out of a total of 38 SUP-related CDI patients. In the PPI group, we could analyze the clinical outcomes of 17 patients among 28 patients with SUP-related CDI. Among them, there was no recurrence and one patient died of CDI-unrelated cause. On the other hand, in the H2RA group, SUP-related CDI was developed in 10 patients. Among them, CDI was recurred in one patients, and another one patient died of CDI-unrelated cause. There was no significant difference in the clinical outcomes between the PPI and the H2RA group, although sample size was too small.

DISCUSSION

Our study evaluated the incidence of CDI in critically ill patients receiving a PPI versus H2RA for SUP. In this retrospective study, we found that the risk of SUP-related CDI was three-times higher in the PPI treatment group than in the H2RA treatment group. The overall incidence of CDI during the gastric acid suppression period in critically ill patients was 3.8% (38/1,005), which is higher than those (0.5% to 1.2%) of previous reports.^{12,17} This discrepancy may be associated with more severe illness in our study population relative to those of previous

studies; the patients enrolled in previous studies were admitted to both ICUs and general wards.^{12,16-18} In addition, considering that the incidence of general health care-associated CDI was 12 per 1,000 patient days,^{19,20} our data confirmed that ICU patients are more vulnerable to CDI than patients on a general ward. Since the occurrence of CDI in critically ill patients is associated with higher mortality, it is important to reduce the development of CDI in these circumstances.

There have been several studies investigating the relationship between PPIs and the incidence of CDI, even in patients without prior history of hospitalization or antibiotic usage.²⁰⁻²² The causes are not clear, but loss of the acidic environment of the stomach caused by PPI use weakens the defense against ingested spores and bacteria, which could be a basis for this association.^{12,17}

Recently, two meta-analysis studies evaluated the effectiveness of PPIs versus H2RAs for preventing UGI bleeding.^{8,11,18} Their results were contradictory. Lin *et al.*⁸ reported that PPIs were not better for preventing UGI bleeding than H2RAs. In contrast, Kim *et al.*¹¹ reported that PPIs were better than H2RAs. The American Society of Health-System Pharmacists guidelines for SUP do not specify which drug to use.²³ In our study, medication for SUP was chosen based on the physician's experience and preference.

Antibiotic exposure is a well-established risk factor for CDI. In the present study, antibiotic use was classified by number and type of antibiotics (cephalosporin, fluoroquinolone, penicillin, vancomycin, and carbapenem). However, we found no association between antibiotic types and the incidence of SUP-related CDI. These results can be explained by the fact that most of the enrolled patients (834/1,005, 83.0%) received antibiotics for a variety of reasons, making it difficult to discern a significant effect of antibiotics use. SUP-related CDI group was received more number of antibiotics than "no CDI group" (92.1% vs 82.6%), although it is not statically significant. Therefore, we think these results do not imply that there is no association between antibiotics use and the development of CDI. Risk factors for the development of CDI identified from the previous studies were antibiotics use, older age, extended hospital stay and immunosuppressive treatment, as well as use of PPIs.^{10,11,16} However, there was no association between above risk factors except PPIs use and the development of CDI in this study.

In our study, DM was an independent risk factor for the development of SUP-related CDI. In most of previous studies published, DM was not a significant risk factor for CDI. Meanwhile, one study examining quinolone-induced CDI showed DM as a risk factor for CDI development.²⁴ Considering that obesity might be a risk factor for CDI²⁵ and DM is a typical obesity-related comorbidity, it might be assumed that DM is related to the occurrence of CDI as a result of obesity-related dysregulation of the immune system, decreased cell-mediated immunity or some other mechanism.²⁵⁻²⁷ On the other hand, in our study, body

mass index was not a risk factor for the development of SUP-related CDI. Adjusting such conflicting results, it is suggested to be needed further study with large sample size.

In the present study, there are several differences in baseline characteristics between the PPI group and the H2RA group (Table 2). The PPI group had higher mean age, longer SUP and more comorbidities than the H2RA group, whereas the H2RA group had longer ICU stay, higher rates of steroid use, mechanical ventilator apply, and mortality, suggesting these differences between two groups might affect the results of our study. However, the multivariate analysis after adjusting confounding factors such as age, comorbidities, and steroid use, demonstrated that PPIs use is an independent risk factor for the development of SUP-related CDI.

Our study has several limitations. First, it was retrospective and we investigated only part of the period of hospitalization, namely from admission to 3 days after discontinuation of SUP. And several other medications might have influenced the occurrence of CDI. Secondly, we could not determine whether PPIs and H2RAs were prescribed for the purpose of SUP in all the enrolled patients. We simply included all patients who did not receive gastric acid suppressants within 2 months of admission and who started these medications in the ICU. And, some of enrolled patients could have taken antibiotics, PPI, or H2RA from other hospitals before admission to ICU. Thirdly, it was unclear what proportion of GI hemorrhage patients were enrolled in this study. Fourthly, the severity of comorbidity may be more important than whether the patient has the comorbidity or not. However, this study did not consider the severities of the comorbidities. Fifthly, in the present study, 40 patients were excluded due to the prior use of antibiotics before admission. The prior use of antibiotics before admission could be a predictive factor for CDI occurrence. Because this study was performed in a retrospective manner, it was difficult to accurately investigate the history of antibiotics use before admission. Lastly, the PPIs were used for a longer period than the H2RAs, which might affect the development of CDI. However, there was no difference in the total period of SUP between the "SUP-related CDI group" and the "no CDI group." To validate our results, further prospective randomized controlled trial with larger sample size is warranted.

In conclusion, PPI therapy in critically ill patients is associated with a higher risk of SUP-related CDI than H2RA therapy, suggesting that clinicians may consider using H2RAs rather than PPIs for SUP in these circumstances.

CONFLICTS OF INTEREST

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

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