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ORIGINAL ARTICLE

Effect of proton pump inhibitors in hospitalization on mortality of patients with hepatic encephalopathy and cirrhosis but no active gastrointestinal bleeding

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KEYWORDS
Cirrhosis;
Hepatic encephalopathy;
Proton pump inhibitor;
Mortality

Summary
Background: Hepatic encephalopathy (HE) is a neuropsychiatric complication of decompensated cirrhosis. Proton pump inhibitors (PPIs), used as potent acid suppressants, are associated with HE occurrence in cirrhotic patients. However, it is still unknown if PPIs contribute to mortality in cirrhotic patients with HE and no active gastrointestinal bleeding.
Methods: We used the Taiwan National Health Insurance Database to identify 1004 cirrhotic patients with HE and no active gastric bleeding, who received oral PPIs between January 1, 2010 and December 31, 2013. On the basis of comorbid disorder data, we used propensity score matching at a 1:4 ratio to select 4016 cirrhotic patients with HE and no active gastric bleeding who did not receive PPIs as a comparison group. All patients were followed up for one year from the index time.
Results: The overall 30-day, 90-day, and 1-year mortalities were 36.1%, 52.6%, and 70.1% in PPI group, and 27.5%, 41.7%, and 62.4% in non-PPI group. Using Cox regression model analysis with adjustment for age, gender, and other comorbid disorders, we obtained hazard ratios of 1.360 (95% CI: 1.208–1.532, $P < 0.001$), 1.563 (95% CI: 1.314–1.859; $P < 0.001$), and 1.187 (95% CI: 1.008–1.398; $P = 0.040$) for, respectively, 30-day, 30-day to 90-day, and 90-day to 1-year mortality in patients taking PPIs.

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Conclusion: PPIs increase short-term and long-term mortality of cirrhotic patients with HE and no active gastrointestinal bleeding.

Introduction

Hepatic encephalopathy (HE), a neuropsychiatric disorder in patients with advanced cirrhosis, is characterized by mental disorders, ranging from minor cognitive dysfunction to lethargy, depressed consciousness, and even coma [1]. Some of the precipitating factors include gastrointestinal bleeding [2], bacterial infection [3], constipation, excessive dietary protein, hypovolemic shock, hypokalemia alkalosis [4,5], surgical portosystemic shunt or transjugular intrahepatic portosystemic shunts [6], hyponatremia [7], and use of opiates or benzodiazepines [8]. Recent studies show that altered gut flora and small-bowel bacterial overgrowth are associated with cognitive impairment in these patients [9,10].

Proton pump inhibitors (PPIs) are potent gastric acid suppressants used for gastroesophageal reflux disease and peptic ulcer treatment [11]. In cirrhotic patients, PPIs have been proven to reduce the size of postbanding ulcers after variceal band ligation [12]. Therefore, PPIs are prescribed to about 46—78% of cirrhotic patients during their hospitalizations [13,14]. However, long-term use of PPIs induces bacterial overgrowth in the small intestine, *Clostridium difficile* infection, and enteric infection [15—19]. In addition, PPIs can lead to gut microbiome changes, including decreased bacterial diversity involving an increase in *Firmicutes*, loss of *Bacteroidetes*, or both [20—22]. Use of PPIs in cirrhotic patients increases the occurrence of spontaneous bacterial peritonitis and increases mortality [14,23—25].

PPI use is associated with HE occurrence, which is PPI dose-dependent in cirrhotic patients [25—27]. A small study even showed that PPIs increased 3-month mortality in HE cirrhotic patients [27]. Though PPIs usage has been associated with active gastrointestinal bleeding in cirrhotic patients, it is unknown whether the increase in mortality is attributable to active gastrointestinal bleeding or PPI itself. To reduce this bias, the present study focused on cirrhotic patients with HE and no active gastrointestinal bleeding. We used the Taiwan National Health Insurance Research Database to enroll a large population of such patients and assess the effect of oral PPIs on their mortality before hospital discharge and their long-term mortality after hospital discharge.

Methods

Database

The Bureau of National Health Insurance (BNHI) in Taiwan established the National Health Insurance (NHI) program in 1995. This program currently covers more than 98% of the Taiwan population. All contracted medical institutions must provide medical records to the BNHI for medical payment. The BNHI and National Health Research Institute (NHRI) established the National Health Insurance Research Database (NHIRD) containing these medical records, and the NHRI can authorize the access of investigators to datasets from the NHIRD for research purposes.

The dataset used in the present study was limited to hospitalized patients in Taiwan identified by specific International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes (see under Study sample). All personal privacy information was removed before we received this dataset. The application and agreement number was 104359. The protocol of this study was approved by the Institutional Review Board of Buddhist Dalin Tzu Chi Hospital (IRB B10403026), which waived the requirement for written informed consent.

Study sample

We selected patients discharged with a main or accessory diagnosis of cirrhosis (ICD-9-CM code 571.5 or 571.2) from January 1, 2010 to December 31, 2013. HE (ICD-9-CM code 572.2) was not diagnosed in cirrhotic patients from subtle signs of the disease, i.e., patients in the present study had an overt form of the disease. In patients with multiple hospitalizations for HE, only first episode data were analyzed. Patients with upper gastrointestinal tract bleeding (ICD-9-CM codes: 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, and 533.6), esophageal variceal bleeding (ICD-9-CM codes: 456.0 and 456.2), panendoscopy examinations, or intravenous PPI treatment during hospitalization were excluded. The defined dosage of omeprazole was 20 mg, rabeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, and esomeprazole 40 mg. The total number of defined doses and total number of hospitalization days were calculated, respectively. The average number of defined doses (aDD) of PPI was defined as ''total number of defined doses of PPI'' divided by ''total number of hospitalization days''. Because of the possible association of oral PPIs at high dose with active or recent gastrointestinal bleeding, patients with an aDD of more than 1 were also excluded.

The cirrhotic patients with HE who received oral PPIs, including esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole were placed in the study group (PPI group). We used one-to-four propensity score matching analysis to select the control group (non-PPI group) and adjust for interference by confounding factors associated with PPI use, including age, gender, alcoholism (ICD-9-CM codes 291, 303, 305.00—305.03, 571.0—571.3), hepatocellular carcinoma (ICD-9-CM code 155.0), ascites (ICD-9-CM code 789.5, or procedure code 54.91), renal function impairment (ICD-9-CM code 584, 585, 586, 572.4, or codes for renal failure procedures), and bacterial infections including pneumonia (ICD-9-CM codes 481—483 and 485—487), liver abscess

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