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EFFECTS OF PROTON PUMP INHIBITORS ON THE DEGREE OF DEVELOPMENT OF LIVER ENCEPHALOPATHY IN PATIENTS WITH LIVER CIRROSIS

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Annotation
In this study, we attempted to determine whether proton pump inhibitor (PPI) use in patients with hepatic encephalopathy was predisposed to more severe stages of hepatic encephalopathy according to West Haven criteria. We found that chronic use of PPIs in patients with cirrhosis of the liver and gastroduodenal pathology was associated with significantly higher mean West Haven criteria for hepatic encephalopathy compared with patients who did not use PPIs. Our data also showed that patients with cirrhosis of the liver receiving PPIs have longer hospital stays, with increased morbidity and mortality during their hospital stay.

Keywords: liver cirrhosis, portal hypertension, hepatic encephalopathy, proton pump inhibitors.

INTRODUCTION

Liver cirrhosis is a late stage of liver fibrosis and is characterized by portal hypertension, which can clinically lead to decompensation in the form of ascites, esophageal / gastric varicose veins, or encephalopathy. Some of the most common sequelae associated with liver cirrhosis are neurological and neuropsychiatric disorders termed hepatic encephalopathy (HE). While in cirrhosis of the liver, PE may develop along with the proliferation of fibrosis in certain stages. But there are additional triggers that can speed it up or make it worse. Well-known triggers include infection, gastrointestinal (GI) bleeding, constipation, and medications such as opioids and benzodiazepines [5]. Other etiologies are mentioned in new studies, including changes in intestinal flora and overgrowth of bacteria in the small intestine [9,10]. More recently, studies have been conducted to investigate the role of proton pump inhibitors (PPIs) in the development of PE in patients with liver cirrhosis. PPIs are commonly prescribed for many diseases of the gastrointestinal tract, most commonly gastroesophageal reflux disease (commonly known as GERD), peptic ulcer

disease, and gastritis [2,11]. In contrast to previous views, recent evidence suggests that STIs have the potential to have multiple adverse effects. PPIs act by decreasing the secretion of stomach acid, which is believed to be protective against acid-related damage to the gastric mucosa [12]. Their ability to protect the lining of the gastrointestinal tract was thought to reduce the incidence of gastrointestinal bleeding in patients with cirrhosis. However, new research suggests that in addition to their direct effects on the stomach, PPIs can affect the composition of the gut microbiome as well as promote the overgrowth of small intestinal bacteria [6,13].

Normally, nitrogenous compounds formed in the intestine merge into the portal system and are filtered by the liver [14, 18]. These compounds then enter the urea cycle and are excreted in the urine. However, in patients with liver disease, ammonia clearance is impaired due to decreased liver function due to increased fibrosis and increased portosystemic shunting, resulting in high levels of ammonia in the bloodstream. When ammonia enters the brain, it is metabolized by astrocytes and converted from glutamate to glutamine by glutamine synthase. The accumulation of glutamine increases intracellular oncotic pressure, leading to cerebral edema. Therefore, given the existing mechanisms, it seems that the level of ammonia has a general neurotoxic effect.

Studies have shown that an increased gastric pH increases the intestinal microflora. In turn, this can lead to an increase in bacterial translocation. Microflora species such as Escherichiacoli, Campylobacterjejuni, Clostridium difficile, Salmonella, Vibriocholerae, and Listeria seem to multiply at high gastric pH [6.13]. In addition, the literature suggests that more severe bacterial proliferation, such as bacterial overgrowth in the small intestine, has also been associated with gastric hypochlorhydria secondary to long-term PPI use. In general, in our opinion, an increase in gastric pH promotes greater intestinal bacterial proliferation. The increased proliferation is not without consequences, as the gut microbiome is one of the leading producers of ammonia in the body and therefore can make patients more susceptible to PE, which we believe is the driving force behind our research.

MATERIALS AND METHODS

This retrospective review of the medical record was carried out in the 2nd Therapy department of the 1st clinic of the Samarkand State Medical Institute and in the Samarkand branch of the Republican Scientific Center for Emergency Medical Aid. Patient records have been revised between September 5, 2019 and June 1, 2021. The study included patients with a hospitalization diagnosis with liver cirrhosis complicated by hepatic encephalopathy.

Eligible patients were 25 years of age or older and had a history of end-stage liver disease or cirrhosis as determined by sequential imaging and / or elastography and liver fibroscan. Patients were on PPIs for at least 30 days prior to hospitalization. Exclusion criteria included pregnancy, liver cirrhosis without minimal signs of PE, refusal to sign a consent form, and concomitant diagnosis associated with non-hepatogenic neuropsychiatric disorders. Using medical records and data from electronic medical records, demographic data (age, sex), degree of PE, assessment of end-stage liver disease, length of stay, etiology of liver cirrhosis, co-infection, ammonia levels, history of bleeding in the last 12 months, etiology were collected PE, ICU stay, and patient expiration. Its severity was determined from the subjective and objective portions of hospital admission records using the West Haven criteria [1-6] .

The main result of the study was the assessment of the degree of PE in PPI users compared with non-users at the time of admission to the hospital and throughout the course of treatment in the hospital. Secondary outcomes included infection rate, gastrointestinal bleeding in the past 12 months, mean ammonia levels, and scores on the admission link test.

Multivariate analysis using a linear regression model, the number relationship test was applied to primary and secondary endpoints to determine statistically significant differences between API users and non-users.

RESULTS

A total of 86 patients were enrolled in this study. All patients were diagnosed with cirrhosis based on imaging studies or elastography and / or liver fibroscan, as well as portal hypertension based on clinical signs, imaging or portal pressure measurements. 68 (79%) of these patients with liver cirrhosis took PPIs (group 1), while 18 (21%) patients with cirrhosis did not take PPIs before registration (group 2). The average age of the patients included in this study was 53.5 years. With regard to gender, men constituted 48 (55.8%) PPI patients (P = 0.143).

The main findings of this study were PE score and hospital admission rates for PPI users versus non-users. The PE score by West Haven criteria was 2.4 in the PPI group versus 1.8 in the non-user group. For the hospital course, several outcomes were analyzed [7-14]. The median length of hospital stay in the PPI group was 8.3 days, compared with 6.5 days in those who did not use the PPI. Twenty-seven patients (31.8%) in the PPI user group required hospitalization in an intensive care unit during an inpatient course, compared with 6 patients in the PPI non-user group (16.7%).

To further determine the effects of long-term PPI use in the cirrhosis population, several secondary outcomes were measured, including infections, serum ammonia levels, and gastrointestinal bleeding. As for infections, 13 patients (5.9%) in the PPI group developed secondary infectious diseases such as pneumonia, spontaneous bacterial peritonitis, etc., compared with 4 patients in the PPI-free group (11.1%). the PPI group on admission to the hospital was significantly higher - 65.9 mg / dL compared to 46.7 mg / dL in the non-PPI group.

DISCUSSION

Because of their effectiveness in suppressing gastric acid secretion, PPIs have become one of the most commonly prescribed drug classes. The first available PPI was Omeprazole, which served as the basis for all other PPIs in its mechanism of action, causing irreversible inhibition of H + / K + ATPase, thus stopping the displacement of hydrogen ions into the gastric lumen. Although many studies have confirmed the safety of PPIs, our study shows that PPI use is associated with worse hospitalization outcomes in patients with cirrhosis.

In this study, we found that hospitalized patients with cirrhosis on PPIs had significantly higher mean West Haven criteria. Using linear regression models, we showed that PPI patients had a higher PE score on the West Haven criteria regardless of age, gender, and / or lactulose use. Other statistically significant differences between the PPI and non-PPI user groups included longer hospital stays. According to patients with a higher grade of HE as well as a longer length of hospital stay.

One of the secondary endpoints in this study was the determination of the risk of infection in patients with cirrhosis of the liver on PPIs. Our data show that patients receiving PPIs may have higher rates of infection with various infections, pneumonia, and spontaneous bacterial peritonitis.

Our article has several limitations. First, since this is a retrospective review, the collection of information is incomplete, especially with regard to the subsequent assessment. Second, because we had an uneven distribution of the number of patients in the PPI use and non-use groups [15-22].

CONCLUSIONS

In conclusion, it should be noted that PPIs are commonly prescribed for many diseases of the gastrointestinal tract, including GERD, peptic ulcer disease and gastritis. They are often used without considering their adverse effects. Our study shows that the use of PPIs in patients with liver cirrhosis is associated with a more severe degree of PE development compared with those who did not take PPIs. Our

data also showed that PPI use in this population was associated with longer hospital stays and a higher percentage of patients requiring ICU admission. We propose to reduce the use of PPIs in the cirrhotic population as a means to reduce episodes of PE. Further randomized controlled prospective studies are needed to confirm this observation.

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