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EFFECTS OF PROTON PUMP INHIBITORS ON HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS

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Abstract:

In our study we determined whether proton pump inhibitor (PPI) use in patients with hepatic encephalopathy predisposes to more severe hepatic encephalopathy with cirrhosis according to West Haven criteria. We found that long-term PPI use in patients with cirrhosis accompanied by gastroduodenal pathology was associated with significantly higher mean West-Haven criteria for hepatic encephalopathy compared with patients who did not use proton pump inhibitors. Our study also showed that cirrhotic patients with clear signs of hepatic encephalopathy receiving PPIs have longer hospital stays, with increased morbidity and mortality during their hospital stay.

Keywords: Hepatic Encephalopathy, Cirrhosis, Proton Pump Inhibitors, Portal Hypertension, Gastroduodenal Pathology, Intestinal Flora.

INTRODUCTION.

Liver cirrhosis is a late stage of hepatic fibrosis and is characterised by portal hypertension, which can clinically lead to decompensation in the form of ascites, esophageal/stomach varices, or/and hepatic encephalopathy. Of the most common effects associated with cirrhosis are neuropsychiatric and neurological disorders, termed hepatic encephalopathy (HE). While in cirrhosis, HE can develop by increasing fibrosis in certain stages. But there are additional factors that may accelerate it or worsen its severity. Well-known triggers include infection, gastrointestinal (GI) bleeding, constipation and drugs used in neurology and psychiatry such as opioids and benzodiazepines[5]. Recently, other etiological factors such as changes in intestinal flora and overgrowth of small intestine bacteria have been increasingly mentioned in new studies[9,10]. Most investigators have noted abnormal small bowel motility in their cirrhotic patients. The orocecal transit time, especially small bowel transit, tends to be prolonged, due to the severity of liver disease (e.g. Child-Pugh class), the presence of small bowel bacterial overgrowth and hepatic encephalopathy, and a history of spontaneous bacterial peritonitis. Several studies, both in the West and in the East, have shown that the gut microbiota is altered in patients with cirrhosis, especially in those with PE. Structural and functional changes in the intestinal mucosa, contributing to increased intestinal permeability to bacteria and their products, are observed in cirrhotic patients, which is considered to be an important pathogenetic factor in a number of complications. The mechanism of intestinal barrier dysfunction in cirrhosis is multifactorial, including alcohol, portal hypertension (vascular hyperaemia and dysregulation), endotoxaemia, local inflammation and, most likely, immunological factors and drugs.

More recently, studies have investigated the role of proton pump inhibitors (PPIs) in the development of HE in cirrhotic patients. Proton pump inhibitors (PPIs) are used by 46-78% of patients with cirrhosis, so it is important to clarify the risk profile of these drugs. HE is a devastating complication of cirrhosis, associated with poor quality of life, high risk of relapse and poor prognosis.The desired effect of a PPI is to reduce gastric acid production and increase gastric pH, but as a side-effect this removal of the gastric acid barrier promotes excessive bacterial growth in the gut. This increases the risk of intestinal bacteria moving to the mesenteric lymph nodes, and from there to the blood and lymph. One possible end result is hyperammonemia and systemic inflammation, which is an important hit in the development of HE in patients with cirrhosis.

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Normally, nitrogenous compounds produced in the intestine are drained into the portal system and filtered by the liver[14,18]. These compounds then enter the urea cycle and are excreted with the urine. However, in patients with liver disease, ammonia clearance is impaired by reduced 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 metabolised by astrocytes and converted from glutamate to glutamine by glutamine synthase. Glutamine accumulation increases intracellular oncotic pressure, leading to cerebral oedema.Thus, given the existing mechanisms, it appears that ammonia levels have a general neurotoxic effect.

Studies have shown that elevated gastric pH contributes to an increase in gut microflora. In turn, this can lead to an increase in bacterial translocation. Microflora such as *Escherichiacoli, Campylobacterjejuni, Clostridiumdifficile, Salmonella, Vibriocholerae* and *Listeria* appear to proliferate 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, we think that increased gastric pH contributes to greater intestinal bacterial proliferation. Increased proliferation is not without consequences, as the gut microbiome is one of the leading producers of ammonia in the body and may therefore make patients more susceptible to HE, which we believe is the driving force behind our research.

MATERIALS AND METHODS.

This retrospective review of medical records was conducted in the Department of Therapy, 1st Clinic, Samarkand State Medical University and in the Samarkand Branch of the Republican Scientific Center for Emergency Medical Care. Patient records were reviewed, from 5 September 2019 to 1 June 2021. Patients with a hospitalizing diagnosis of cirrhosis complicated by hepatic encephalopathy were included in the study.

Eligible patients were over 25 years of age, had a history of end-stage liver disease or cirrhosis as determined by serial imaging and/or elastography and liver fibroscan. Patients had been on a PPI for at least 30 days prior to admission. Exclusion criteria included pregnancy, cirrhosis without minimal signs of PE, refusal to sign consent and concomitant diagnosis of non-hepatogenic neuropsychiatric disorders. Using medical records and data from electronic medical records, demographic data (age, gender), degree of HE, evaluation of end-stage liver disease, length of stay, etiology of cirrhosis, concomitant infection, ammonia levels, bleeding history in the past 12 months, etiology of HE, ICU stay and patient expiration were collected. Its severity was determined by the subjective and objective parts of the hospital admission records, using the West Haven criteria.

The primary outcome of the study was an assessment of the degree of HE in PPI users compared with non-users at the time of admission to hospital and throughout the course of hospital treatment. Secondary outcomes included the incidence of infection, gastrointestinal bleeding during the past 12 months, mean ammonia levels and an estimate of the number correlation test at admission.

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

RESULTS: A total of 86 patients were included in this study. The mean age of the patients included in this study was 53.5 years. In terms of gender, 48 (55.8%) patients were male.All patients had a confirmed diagnosis of cirrhosis based on imaging studies or liver ultrasound, elastography, liver fibroscan, and evidence of portal hypertension based on clinical signs, imaging or portal pressure measurement. Sixty-eight (79%) of these cirrhotic patients were taking PPIs (group 1), whereas 18 (21%) cirrhotic patients were not taking PPIs (group 2).

The main outcomes of this study were the assessment of HE and the duration of use of PPI users compared with non-users. The West-Haven score for HE was 2.4 in the PPI group compared to 1.8 in the PPI non-users group. With regard to the hospital course, several outcomes were analysed. The mean length of hospital stay was 8.3 days in the PPI group compared to 6.5 days in the non-PPI group. Twenty-seven patients (31.8%) in the PPI user group required hospital admission to the intensive care unit during the inpatient course compared to 6 patients in the non- PPI user group (16.7%).

Several secondary outcomes, including infections, serum ammonia levels and gastrointestinal bleeding were measured to further determine the consequences of long-term PPI use in the cirrhotic patient population. Regarding infections, 13 patients (5.9%) in the PPI group developed secondary infections like pneumonia, spontaneous bacterial peritonitis, etc. compared to 4 patients in the non- PPI group (11.1%).The mean ammonia level at admission to hospital was significantly

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higher-65.9 mg/dL compared to 46.7 mg/dL in the non-PPI group.

OBSERVATION:

The effectiveness in inhibiting gastric acid secretion has made PPIs one of the most commonly prescribed medicines. Although many studies have confirmed the safety of PPIs, our study shows that in patients with cirrhosis, PPI use is associated with poorer hospital outcomes.

PPIs are commonly prescribed for many gastrointestinal conditions, most commonly gastroesophageal reflux disease, peptic ulcer disease and gastritis[2,11]. In contrast to previous beliefs, recent evidence suggests that PPIs have potentially numerous adverse effects, one of which is the worsening stage of hepatic encephalopathy. PPIs act by reducing gastric acid secretion, which is thought to be protective against acid-related damage to the gastric mucosa[12]. Their ability to protect the gastrointestinal mucosa was thought to reduce gastrointestinal bleeding in patients with cirrhosis. However, new research suggests that, in addition to their direct effect on the stomach, PPIs may also affect the composition of the intestinal microbiome and promote the overgrowth of small-bowel bacteria[6,13]. In this study, we found that hospitalised patients with cirrhosis on PPIs had significantly higher mean West Haven criteria. Using linear regression models, we showed that patients using PPIs had higher West Haven criteria scores for HE regardless of age, gender, and/or lactulose intake. Other statistically significant differences between the PPI-user and non-user groups included longer length of hospital stay. Consistent with patients having a higher degree of PE, as well as a longer duration of hospital stay.

CONCLUSIONS.

In conclusion, proton pump inhibitors are often used without regard to their adverse effects in hepatology. Our study shows that PPI use in cirrhotic patients is associated with a more severe degree of PE compared to those who did not take PPIs. Our data also showed that PPI use in this group of patients was associated with a longer hospital stay and a higher percentage of patients requiring ICU admission. We suggest that PPI use in patients with cirrhosis should be reduced as a means of reducing episodes of HE.

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