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Original Article

Duration of Using Proton Pump Inhibitors as a Risk Factor of Hepatic Encephalopathy in Patients with Cirrhosis

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ABSTRACT

Background:
In patients with cirrhosis use of proton pump inhibitors (PPIs) may increase the risk of infection including spontaneous bacterial peritonitis. Also, in some studies PPIs usage had significant relationship with the severity of cirrhosis and development of hepatocellular carcinoma. In recent studies the relationship between PPIs usage and hepatic encephalopathy had been considered. The aim of this study was to assess the relationship between PPIs and hepatic encephalopathy for investigating their effects in the treatment of patients with cirrhosis.

Materials and Methods:
In this study, 61 patients with liver cirrhosis were evaluated. The patients were followed up in two groups: patients with hepatic encephalopathy and patients with other complications.

Results:
PPIs usage and also the type and dosage of these drugs were not statistically different between the two groups. The duration of PPIs usage in the patients with hepatic encephalopathy was 23 ± 5.72 months and in the second group was 13.04 ± 3.061 months (p = 0.039).

Conclusion:
In patients with cirrhosis, PPIs consumption for a long period, increases the risk of hepatic encephalopathy.

Keywords: Proton pump inhibitors, Hepatic Encephalopathy, Cirrhosis

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INTRODUCTION

Hepatic failure is a condition in which liver loses its metabolic and producing function. It has two types: acute and chronic. Chronic failure or cirrhosis is a condition in which liver loses its physiological function due to long-term liver damage. There are many causes for cirrhosis (1).

Complications of cirrhosis can be edema, ascites, encephalopathy, gastrointestinal bleeding, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, hepatopulmonary syndrome, and others.

Hepatic encephalopathy symptoms include dizziness, altered state of consciousness, and coma, which are caused by chronic liver failure. In advanced stages, it is called hepatic coma, which can lead to death (2). The

cause of this condition is the accumulation of toxins in the blood, which are normally eliminated from the body by the liver. Diagnosis of the condition requires evaluating impaired liver function and ruling out other causes. Blood tests (ammonia levels) may be helpful in the diagnosis.

The first stage of hepatic encephalopathy is determined by the disruption of the sleep-wake cycle. The second phase includes personality changes. In the third stage, confusion is prominent, and the fourth stage is characterized by progressive coma. The underlying causes of hepatic encephalopathy are nitrogen overload, metabolic or electrolyte abnormalities, medications, infections, and unknown causes (20-30% of cases) (2).

Proton pump inhibitors (PPIs) are a group of drugs that their main action is reducing gastric acid. PPIs are among the world's best-selling drugs. This group of drugs is prescribed for the treatment of dyspepsia (3,4), peptic ulcer disease (5), gastroesophageal reflux disease (6), Barrett's esophagus (7), eosinophilic esophagitis (8), and gastrinoma (9). Despite widespread usage, evidence to approve the quality of these drugs is variable. PPIs are generally well tolerated and the incidence of serious short-term complications is very low. There is less information about the effects of long-term PPIs usage (10).

In patients with cirrhosis, PPIs usage may increase the risk of infection including SBP (11,12). But there is no strong evidence to show whether PPIs deteriorate the prognosis of patients with SBP or not (13,14). Also in some studies PPIs usage had significant relationship with the severity of cirrhosis and development of hepatocellular carcinoma (15). In recent studies the relationship between PPIs usage and hepatic encephalopathy had been considered (16).

The aim of this study was to assess the relationship between PPIs and hepatic encephalopathy to investigate their effects in the treatment of patients with cirrhosis.

MATERIALS AND METHODS

This was a cross-sectional study, in which, 61 patients with liver cirrhosis who were diagnosed and treated in Imam Khomeini Hospital in Tehran, were evaluated. The patients were followed up in two groups: patients with hepatic encephalopathy and patients with other complications. The patients were excluded if they had other complications of cirrhosis in addition to hepatic encephalopathy. The minimum duration of PPIs usage for inclusion in this study was one month. The patients were also excluded if there were other causes for PPIs usage other than cirrhotic complications.

In this study demographic characteristics such as age, and sex, and also clinical characteristics including history of cirrhotic complications, lab data, and history of gastrointestinal problems such as dyspepsia, and reflux and also the drug history (especially PPIs) with dosages and duration of use were recorded and then the data were analyzed by using SPSS software version 16.

The Model for End-Stage Liver Disease (MELD) score was used to calculate the severity of cirrhosis. MELD is a measure for ranking and rating the severity of cirrhosis. This score can be useful to determine and prioritize patients for transplantation and is based on the parameters of serum bilirubin, serum creatinine, and INR (International Normalized Ratio). In this study this score was used for determining the severity of cirrhosis.

RESULT

In our study 61 patients were evaluated and divided into two groups; 35 patients with encephalopathy and 26 patients with other complications of cirrhosis. There were 40 (65.4%) men and 21 (34.4%) women. The mean age of the patients was 53.91 (±15.61) years. The mean age in patients with encephalopathy was 57.2 (±13.45) years and in the group with other complications of cirrhosis was 49.50 (±17.42) years. The difference was not statistically significant ($p > 0.05$).

The mean of the MELD score was 21.57 ± 8.39 in patients with encephalopathy and 18.31 ± 6.17 in the second group with no statistically significant difference between the two groups ($p > 0.05$).

The frequencies of the complications of cirrhosis were as follows: ascites in 8 cases (13.1%), SBP in 5 cases (8.2%), encephalopathy in 35 cases (57.4%), and gastrointestinal bleeding in 13 patients (21.3%).

In order to assess the effect of PPIs in the development of hepatic encephalopathy in patients with cirrhosis, the patients were divided into two groups with encephalopathy and with other cirrhotic complications. The usage of PPIs and also the type and dosage of these drugs were assessed in the two

Table 1: Usage and duration of using proton pump inhibitors in patients with and without encephalopathy

Variables	Proton pump inhibitors			Total number
	Used		Not used	
	Number	Duration of usage (months)	Number	
Encephalopathy	18	23 ± 5.72	17	35
Other complications	13	13.04 ± 3.061	13	26

groups. In our study there was not statistically significant relationship between the two groups (table 1). The most common cause of PPIs usage in the patients was dyspepsia.

The relationship between the incidence of hepatic encephalopathy and the duration of using PPIs was assessed. The duration of PPIs usage in the patients with hepatic encephalopathy was 23 ± 5.72 months and in the second group was 13.04 ± 3.061 months. This difference was statistically significant ($p = 0.039$).

In order to assess the effect of the history of cirrhotic complications (including encephalopathy, gastrointestinal bleeding, SBP, and ascites) in the development of hepatic encephalopathy in patients with cirrhosis, the data were analyzed in the two groups. These past cirrhotic complications were significantly predisposing factors for hepatic encephalopathy ($p < 0.001$), ($p < 0.01$), ($p < 0.05$), and ($p < 0.05$).

DISCUSSION

Cirrhosis is an important leading cause of death worldwide. Studies have shown that mortality is more in men than women because of cirrhosis (17). In terms of prevalence studies, the most common complication of cirrhosis is ascites. Hepatic encephalopathy is in the second rank (18). However, in our study the most common complication was hepatic encephalopathy, which could be due to the type of the patients' population; because most of the patients in our study were hospital inpatients.

Many studies that had been done on the relationship between SBP and taking PPIs, have shown that PPIs usage can be proposed as a risk factor for the development of SBP. For example, Silpe and his colleagues and Bajaj and co-workers had shown a strong association between PPIs usage and the risk of SBP (19,20). However, some other studies reported conflicting results that the relationship between PPIs usage and the risk of SBP had not been found in them (21).

Lin and his colleagues in a study in 2014, compared 55 patients who had hepatic encephalopathy during their hospital admission with 110 patients with acute on chronic liver failure in the setting of hepatitis B infection without hepatic encephalopathy. The usage of PPIs was considered as a risk factor in patients with hepatic encephalopathy (16). In their study, the researchers had not assessed the type and duration of using PPIs among their patients.

Also, Dam and his colleagues in 2016, assessed the effect of PPIs on hepatic encephalopathy or SBP based on information that had extracted from three randomized controlled trials (RCTs). Of 865 patients with cirrhosis who were evaluated, PPIs usage was between 30% and 39%. The result of that study showed that PPIs could be considered as a risk factor for hepatic encephalopathy and SBP (22). In that study the association between PPIs usage and severity of cirrhosis based on the MELD score was not significant. However, in the study by Dultz and his colleagues in 2015, PPIs usage was significantly associated with disease severity and higher MELD score (15). In our study, there was not any significant correlation between consumption or non-usage of PPIs and severity of disease in our patients.

Ultimately, in our study there was not any association between the usage of PPIs and the incidence of hepatic encephalopathy. However, for the first time, a significant correlation between the duration of PPIs usage and the risk of hepatic encephalopathy was found. This means that if the patients use PPIs for a long time, the risk of hepatic encephalopathy increases. Also, in this study the significant relationship between a history of complications of cirrhosis and the current incidence of hepatic encephalopathy was detected.

We hope that the results of this study indicate the necessity of careful selection of PPIs, especially in patients with cirrhosis and monitoring of the treatment in order to minimize the complications related to these medications.

CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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