Original Article

Association of Proton Pump Inhibitors with Hepatic Encephalopathy among Patients with Liver Cirrhosis

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ABSTRACT

Objective: To find an association between PPIs and increased risk of hepatic encephalopathy in cirrhosis.
Study Design: Case-Control study
Place and Duration of Study: This study was conducted at the conducted in the department of Medicine and gastroenterology, Ayub Teaching Hospital; Abbottabad from August 2019 to June 2020 for a period of 10 months.
Materials and Methods: All patients with liver cirrhosis and hepatic encephalopathy presenting to the department of medicine and gastroenterology were included through a non-probability consecutive sampling.
Results: A total of 166 patients with liver cirrhosis were enrolled in the study including 93 (56.0%) male and 73 (44.0%) female patients. The mean age of the patients was 59.00±9.789 years. A total of103(62.0%) patients were found PPIs users and 63(38.0%) were found PPI nonusers. Patients using PPIs were 4 times more likely to develop Hepatic Encephalopathy as compared to those patients of liver cirrhosis who were not using PPIs (OR= 4.276, CI= 2.172-8.420).
Conclusion: Patients with liver cirrhosis who are using proton pump inhibitors are more likely to develop hepatic encephalopathy when compared to the control group.
Key Words: Proton Pump Inhibitors, Hepatic Encephalopathy, Liver Cirrhosis

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INTRODUCTION

Liver cirrhosis has emerged as a major cause of morbidity and mortality and affected about 2.8 million people worldwide and resulted in 1.3 million deaths in 2015.[1] In the developing countries, liver cirrhosis and its complications are a major health problem. Hepatic encephalopathy, a major complication of cirrhosis, has an estimated prevalence of 22–74% in USA.[2] Prevalence of hepatic encephalopathy in Pakistan is 63.4%.[3] Infection and upper gastrointestinal bleeding are major precipitating factors for hepatic encephalopathy. About 30% of patients with cirrhosis die due to hepatic encephalopathy.[4]

One year survival rate is 36% after onset of hepatic encephlopathy.[5]

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Proton pump inhibitors (PPIs) are widely used (78.3%) in cirrhosis to prevent bleeding associated with portal hypertension.[6] PPIs, by reducing acid secretion, can increase the risk of gastrointestinal infections by raising pH of stomach and making it more prone to colonization by various pathogenic bacteria.[7] PPIs may increase absorption of gut-derived nitrogenous substances because of its effect on retarding gastrointestinal motility, delaying gastric emptying rate and decreasing gastric mucus viscosity. Increased ammonia-producing enteric bacteria in patients is shown to be a risk factor for hepatic encephalopathy.[8]

In past, many trials have been conducted under different circumstances concerning the association of PPIs with hepatic encephalopathy in patients with liver cirrhosis. The available data is conflicting. In a case–control study by Tsai CF,[9] approximately 38% of cirrhotic patients with HE and 21% of patients without HE were taking defined PPIs. They concluded that PPI's are associated with increased hepatic encephalopathy (adjusted odds ratio was 1.738) while in a study by Dam G,[10] cumulative risk HE was 31% for those who used PPIs at baseline versus 25% for those who did not and the adjusted odds ratio was 1.36 ($p>0.05$).[11] The results of these two studies had shown variable results with Tsai CF establishing that using PPI is associated with higher risk for hepatic encephalopathy, where Dam G, et al concluded that there exist no association

with hepatic encephalopathy among patients with liver cirrhosis.

Liver cirrhosis is becoming an epidemic in Pakistan due to high prevalence of hepatitis B and C in our community i.e. 7.6%.[12] On the other hand, proton pump inhibitors are also frequently used in such patients. So, the relationship between PPI use and hepatic encephalopathy should be well-defined. Because cirrhosis, hepatic encephalopathy and widespread use of PPI are widely prevalent in our population, there is a dire need for assessing causal relationship if any. This study was conducted to find an association between use of PPIs and increased risk of hepatic encephalopathy in cirrhotic patients. There is a paucity of data in our region so the present study was designed with an aim to generate evidence so as to provide guidance to healthcare practitioners for careful prescription of PPI's in patients with liver cirrhosis.

MATERIALS AND METHODS

This case control study was conducted in the department of medicine and gastroenterology of a tertiary care hospital over a period of one year (1st August 2019 to 31st July 2020). Sample size was calculated by using the WHO software for sample size calculation taking confidence Level of 95% with Exposure Rates in Cases (use of PPI) = 38%[9] and Exposure Rates in controls (use of PPI) = 21%[9] and Relative Precision of 5%. A total of 166 patients with liver cirrhosis were included through a non- probability consecutive sampling after the approval of research and ethical committee of the institute. Informed consent was obtained and demographic profile (age, gender and contact) was noted. The patients with HE in liver cirrhosis were labeled as cases(n=83), and patients without HE in liver cirrhosis were labeled as controls(n=83). All the patients were evaluated for detection as PPI user (yes or no) as per operational definition in both groups. Data was entered on a structured proforma.

Cases were defined as patients of either sex between 30-70 years of age presenting with hepatic encephalopathy and admitted for the last 6 days, while controls were of the same characteristics with liver cirrhosis but without encephalopathy. Patients with HAV, HDV, HIV and CMV along with hepatocellular carcinoma, history of gastrointestinal bleeding or psychiatric illness were excluded from both case and controls.

The data was entered and analyzed in SPSS version 20.0. Mean and standard deviation was calculated for quantitative variables like age. Frequencies and percentages were calculated for categorical variables like gender and age groups. Odds ratio was calculated to measure association between proton pump inhibitors and hepatic encephalopathy among cirrhotic patients and calculating 95% confidence interval for ORs.

RESULTS

A total of 166 patients were enrolled into this study and were equally divided into cases and controls as per definition. Out of 166 patients, 93 (56.0%) were male and 73 (44.0%) were female. Mean age of the participants was 59.00±9.789 years. Patients were further divided into two age groups. A total of 136(81.9%) patients were found in age group of 51 to 70 years and 30(18.1%) were in age group of 30 to 50 years. Out of the total study population, 103(62.0%) were PPIs users and 63(38.0%) were PPI nonusers (Table 1). Patients were stratified on the basis of PPI usage. In the age group 30 to 50 years, 19(11.4%) were using PPI while 11(6.6%) were not. While in the age group 51 to 70 years, 84(50.6%) were PPI users and 52(31.3%) were nonusers. Among the male participants, 58(34.9%) were PPIs users and 35(21.1%) were nonusers while among females, 45(27.1%) were PPIs users and 28(16.9%) were nonusers (Table 2). The data analysis revealed that male patients with liver cirrhosis using PPIs were 1.09 times more likely to develop Hepatic Encephalopathy than female (OR= 1.09, CI= 0.37-3.18) (table 3). The association of hepatic encephalopathy in cirrhotic patients was assessed with respect to proton pump inhibitors usage. Among cases, 65(39.2%) patients were PPIs users and 18(10.8%) were non users while in controls 38(22.9%) patients were PPIs users and 45(27.1%) were non users. The patients with liver cirrhosis using PPIs were more than 4 times likely to develop Hepatic Encephalopathy as compared to those patients of liver cirrhosis who were not using PPIs (OR= 4.276, CI= 2.172-8.420) (Table 4).

Table No.1: Patient characteristics (n=166)

Mean age in years	59.00±9.789	
Mean age in years (Male)	60.80±8.350	
Mean age in years (Female)	56.71±11.001	
Gender	No. of Patients	Percentage
Male	93	56%
Female	73	44%
Total	166	100%
Age Groups		
30 to 50 years	30	18.1%
51 to 70 years	136	81.9%
Total	166	100%
PPI Usage		
PPI Users	103	62%
PPI nonusers	63	38%
Total	166	100%

Table No.2: Age group and gender wise distribution in relation to PPI Usage

Age group	PPI users	PPI Nonusers	Total
30 to 50 years	19 (11.4%)	11 (6.6%)	30 (18.1%)
51 to 70 years	84 (50.6%)	52 (31.3%)	136 (81.9%)
Total	103 (62.0%)	63(38.0%)	166(100%)
Gender			
Male	58 34.9%	35 (21.1%)	93 (56%)
Female	45 27.1%	28 (16.9%)	73 (44%)
Total	103(62%)	63 (38%)	166 (100%

Table No.3: Association of gender to PPI usage in patients with hepatic encephalopathy in Cirrhosis

Gender	Hepatic encephalopathy with liver cirrhosis		Total	Odds ratio	CI
	PPI User	PPI Non user			
Male	41	11	52	1.09	0.37-3.18
	49.39%	13.25%	62.6%		
Female	24	7	31		
	28.9%	8.4%	37.3%		
Total	65	18	83		
	78.31%	21.68%	100.0%		

Table No.4: Association of Hepatic encephalopathy to PPI usage in patients with cirrhosis

Liver Cirrhosis	PPIs		Total	Odds ratio	CI
	user	Nonuser			
HE among liver cirrhosis	65	18	83	4.276	2.172-8.420
	39.2%	10.8%	50.0%		
Without HE among liver cirrhosis	38	45	83		
	22.9%	27.1%	50.0%		
Total	103	63	166		
	62.0%	38.0%	100.0%		

DISCUSSION

Liver cirrhosis and its complications like hepatic encephalopathy have emerged as a major cause of morbidity and mortality worldwide. Studies have reported that PPIs use is positively associated with increased incidence of hepatic encephalopathy in patients with liver cirrhosis thus, potentially complicating the management of liver cirrhosis.

Our study showed a slight preponderance of male patients (56% males vs 44% females). The frequency of PPI users was higher than nonusers. Similar results are reported in literature while assessing hepatic encephalopathy in cirrhotic patients in PPIs users and nonusers in the study conducted by Tsai CF, et al.[9] In our study, the stratification by age showed that the majority of patients were in age group of 51-70 years. Of these, nearly half of the patients were PPI users 30 In another study, almost same results were reported regarding PPIs users and nonusers having cirrhosis with hepatic encephalopathy in the study conducted by Tapper EB et al. [12]

Our study demonstrated slightly higher number of male patients with hepatic encephalopathy using PPI (OR=1.09). In another study by Dam G et al, almost similar results have been reported[10]. Our study showed that a significantly higher number of patients with liver cirrhosis who were using PPI developed hepatic encephalopathy (OR=4.276). Similar results are reported in literature by Zhu et al where Proton Pump Inhibitor use in cirrhotics was significantly higher in patients with hepatic encephalopathy[13]. 128 In another study by Lin et al the PPI usage was higher in patients having hepatic encephalopathy with liver cirrhosis[14]. A meta-analysis encompassing nine studies reported a 2.08 fold greater chances of development of hepatic encephalopathy among PPI users[15]. Another study from Italy reported the association of PPI usage with development of hepatic encephalopathy and consequent decreased survival in patients with liver cirrhosis[16].

CONCLUSION

The patients with Liver cirrhosis who are taking PPIs are at an increased risk of developing Hepatic encephalopathy. Hence, proton pump inhibitors should be prescribed to patients with liver cirrhosis with great caution. This study has its own limitations as it was a single- center based study of a small sample size in our specific population, therefore the results cannot be generalized on general population.

Author's Contribution:

Concept & Design of Study:	Syed Yasir Hussain Gilani
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Final Approval of version:	Syed Yasir Hussain Gilani

Conflict of Interest: The study has no conflict of interest to declare by any author.

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