Original Article

Comparison of Frequency of Upper Gastrointestinal Bleeding With and Without the Use of Proton Pump Inhibitors in Patients of Chronic Kidney Disease Undergoing Hemodialysis

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ABSTRACT

Objective: To analyze the effect of proton pump inhibitors (PPIs) on incidence rate of upper gastrointestinal tract bleeding (UGIB) in patients with chronic kidney disease undergoing hemodialysis.

Study Design: A retrospective cohort study

Place and Duration of Study: This study was conducted at the Nephrology department of Nishtar Medical University & Hospital Multan from 22nd June 2020 to 22nd Dec 2020.

Materials and Methods: Clinical data of 300 patients suffering from end-stage renal disease and who began hemodialysis between 2015 to 2020 was categorically reviewed. The study compared the incidence of upper gastrointestinal tract bleeding in 80 patients treated with PPIs to another 220 patients who didn't undergo this treatment (control group).

Results: 41 patients had UGIB during the study period, at the rate of 14.4 per 1000 persons per year. In the patients given anti-platelet or warfarin therapy, the incidence was 20.7 per 1000 persons per year. A meantime of 26.3± 29.6 months was found between the start of dialysis and the appearance of UGIB. Kaplan-Meier analysis revealed a significantly lower probability of UGIB occurrence in PPI group as compared to control group. Univariate analysis demonstrated an association of anti-platelet and anti-coagulation, PPI use, and coronary artery disease with UGIB. After adjusting confounding variables involved in the potential occurrence of UGIB, PPI was highly effective in lowering UGIB when compared with the control group.

Conclusion: Treatment of patients with chronic renal disease undergoing dialysis with PPIs leads to reduced occurrence of UGIB.

Key Words: Dialysis, Chronic Renal Disease, Proton Pump Inhibitor

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INTRODUCTION

Bleeding complications are highly prevalent in end-stage renal disease (ESRD)[1]. Upper gastrointestinal bleeding (UGIB) mainly occurs in dialysis patients, it is related to increased risk of mortality and rebleeding compared to the normal population[2].

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Pathogenesis and origin of UBIG have not been explained, though anaemia, platelet dysfunction and abnormal blood coagulation may lead to bleeding[3]. As hemodialysis patients (HD) are constantly exposed to anticoagulants, they have more tendency of UGIB as compared to patients undergoing peritoneal dialysis (PD) [4]. With time there has been a decline in the prevalence of UGIB in the general population. However, according to a study among ESRD patients, the incidence of UGIB has not been lowered in last 10 years[5]. As per estimates, 3% to 7% mortality in ESRD patients is due to UBIB. There are multiple strategies for reducing UGIB; among these, proton pump inhibitors have been proven significant and are recommended for high-risk UGIB patients who take non-steroidal anti-inflammatory drugs (NSAIDs), aspirin and dual anti-platelet therapy[6].

Increased administration of acid-suppressive regime in ESRD patients leads to an increase in gastrointestinal (GI) symptoms[7]. Among patients undergoing PD and HD, frequencies of GI disease were 9.3% and 10.1%[8].

PPIs are safe for administration in ESRD patients and, when given with acid suppression therapy, rarely results in adverse effects. Studies show that in patients with GI disease, low dose PPIs are being increasingly prescribed. In this study, we will assess the effect of proton pump inhibitors (PPIs) on the incidence rate of upper gastrointestinal tract bleeding (UGIB) in patients with chronic kidney disease undergoing hemodialysis.

MATERIALS AND METHODS

A retrospective cohort study was conducted at the Nephrology Department of Nishtar Medical University & Hospital Multan for 6 months. Clinical data of 300 patients suffering from end-stage renal disease and who began hemodialysis between 2015 to 2020 was categorically reviewed. All the included patients underwent upper gastrointestinal endoscopy for GI symptoms. Those below 18 years, had a renal transplant, had a history of peptic ulcer and gastric surgery, liver cirrhosis, malignancy, less than three months of dialysis, less than six months follow up duration and those prescribed NSAIDs,corticosteroid and histamine H2-receptor antagonist were excluded. Subjects were divided in two groups: the first group contained those who were given PPIs, and the second (control group) contained those who were not being prescribed PPIs. The study was approved by the ethics committee of the hospital.

Diagnosis done by gastroenterologist and absence of any other bleeding pathology was considered as UGIB. If an ESRD patient was a suspect of clinical GI bleeding like melena, idiopathic decrease in haemoglobin>2g/dL, hematochezia or hematemesis, endoscopy was performed by a gastroenterologist. Bleeding was defined as the presence of visible vessels, bleeding in the stomach, adherent clot and high-risk stigmata in endoscopic findings. Subjects with gastric varices or oesophagal bleeding were not included in the study. Repeating endoscopy due to doubt of rebleeding and the occurrence of stigmata in the stomach was defined as rebleeding.

SPSS version 18.0 was used for performing a statistical analysis. Data was ranged and represented as median or mean ± SD. Analysis of continuous data was done using Student's t-test or Mann-Whitney U test for equal or unequal variance respectively, and Pearson's χ^2 test was used for investigating categorical variables. Kaplan-Meier survival estimates were used for estimating cumulative non-bleeding rates in both groups, and the difference between the curves was estimated using the log-rank test. Independent predictors of UGIB were evaluated using Cox's proportional hazard model analysis. P-value less than 0.05 was considered statistically significant.

RESULTS

In this study, clinical data of 300 patients suffering from end-stage renal disease and who began hemodialysis between 2015 to 2020 were retrospectively reviewed. The clinical and demographic data of the cohort include: mean age= 63 ± 14 years, male=69%, patients undergoing hemodialysis =94%, diabetics= 65%, smokers=2 %. 86 patients had coronary artery disease, 167 were given aspirin, 15 were given warfarin, and 32 were treated with dual anti-platelet therapy. Out of 300 patients, 80 were in the PPI group (50 patients were given pantoprazole orally 20 mg once daily and 30 were given rabeprazole 10 mg once daily orally), and 220 were in the control group. The difference in sex, age, mode of dialysis, renal disease, smoking, body mass index (BMI), and anti-platelet and warfarin use between both the groups was not significant. The basic characters of groups are mentioned in Table 1.

Table No.1: Basic Characters Of Groups

Characteristics	PPI group	Control group
Age (years)	64.8±13.8	63.6±14
Follow up (month)	56.8±34.6	67.5±38.5
Sex, male	50 (62.5)	157 (71.4)
Hypertension	51 (63.7)	167 (76.0)
Diabetes	49 (61.2)	148 (67.3)
Smoking	5 (6.25)	1 (0.45)
Hemodialysis	72 (90)	210 (95)
BMI (kg/m2)	24.3±4.1	24.4±4.6
History of cardio vascular events		
Cerebrovascular event	17 (21.25)	29 (13.18)
Coronary heart disease	25(30.86)	58 (26.36)
Chronic liver disease	1 (1.25)	4 (1.81)
Aspirin use	62 (77.5)	165 (75)
Dual anti-platelet therapy	9 (11.25)	22 (10)
Warfarin	2 (2.5)	4 (1.81)
Helicobacter pyroli		
Positive	20 (25)	30 (13.36)
No test	60 (75)	190 (86.36)
Basic laboratory tests		
Haemoglobin (g/L)	9.2±1.7	8.8±1.7
Hematocrit (%)	27.4±5.4	25.1±4.1
Creatinine (mmol/L)	6.8±3.9	7.1±3.1
Protein (g/L)	7.4±.8	7.1±.8
Albumin (G/L)	3.1±.8	2.9±.5
C-reactive protein(mg/L)	10.0±17.8	9.5±16.2
Death	5	24

41 patients had UGIB during the study period, at the rate of 14.4 per 1000 persons per year. In the patients given anti-platelet or warfarin therapy, the incidence was 20.7 per 1000 persons per year. The mean duration between UGIB events and the start of dialysis was 26.3± 29.6 months. Sources of UGIB are mentioned in Table 2. Among ESRD patients the most common cause of UGIB was gastric lesions, accounting for half of the bleeding sources. 18 patients came with hematochezia or melena, 13 patients came with hematemesis, while endoscopy was performed on 10 patients because of idiopathic anaemia. At the time of

admission, haemoglobin level was 6.6 ± 1.8 g/dL, and red cell transfusion was given to 40 patients. Rebleeding occurred in 2 patients, 1 in each group. 1 death occurred in the control group due to UGIB.

Table No.2: Causes

Cause	Subjects
Gastric Ulcer	13
Duodenal Ulcer	8
Duodenal and Gastric Ulcer	2
Dieulafoy's Lesion	5
Mallory-Weiss Tear	4
Gastric Erosion	4
Duodenal Erosion	4
Gastric cancer	1

The frequency of anti-platelet therapy and warfarin use was significantly higher in patients with UGIB as compared to those without it. 2 patients in the PPI group and 39 in the control group had bleeding. According to Kaplan Meier analysis possibility of UBIG was much less in the PPI group as compared to the control group. According to the subgroup analysis, the use of PPI with anti-platelet or warfarin therapy risk of PPI was decreased significantly.

According to the Univariate analysis, anti-platelet and warfarin therapy, no use of PPI and coronary artery disease were related to UGIB. After adjusting sex, age, hypertension, coronary heart disease, diabetes, smoking, mode of dialysis, albumin and haemoglobin, use of PPI significantly reduced UGIB. Table 3.

Table No.3: Univariate analysis

Variable	HR	95% CI	P-value
PPI	14.688	1.83-101.63	.011
Warfarin	5.728	1.56-14.24	.005
Anti-platelet therapy	2.456	1.37-1.43	.002
Coronary artery disease	2.077	.953-4.531	.093
Cerebrovascular disease	1.591	.973-2.286	.066
Smoking	2.154	.658-7.042	.203
Diabetes	1.021	.47-2.2	.898
Hypertension	1.418	.58-2.91	.496
Age	1.001	.97-1.02	.87

DISCUSSION

In this study, it was found that ESRD patients had a relatively high incidence of UGIB, which was significantly reduced upon the administration of PPIs. In this study, incidence of UGIB among ESRD patients was 14.4 per 1000 person per year and duration from the start of dialysis to UGIB was 26.3± 29.6 months. In the PPI group, the incidence of UGIB was much lower as compared to control group. These effects were similar in the patient's given warfarin or anti-platelet therapy. Results indicate that in patients with ESRD, administration of PPIs lowers the incidence of UGIB events.

Dialysis patients are at a higher risk of UGIB as compared to the normal population. A study conducted in the United States shows that in ESRD patients incidence of UGIB was 22.8 per 1000 person-year[9], which is higher than the incidence in the PPI group and the same as incidence in control group. Another study showed that in HD patients incidence of UGIB was 42.0 per 1000 person per year, which is more than incidence in this study[1]. The results are associated with the exclusion of patients given steroids or NSAIDs and liver cirrhosis patients and inclusion of patients undergoing peritoneal dialysis. Though there is uncertainty regarding risk factors associated with UGIB in ESRD patients, it was found that administration of anti-platelet drugs and warfarin therapy are significantly related. A study revealed that inability to move and history of cardiovascular and smoking are related to an increased risk of UGIB[10]. Another study showed UGIB is significantly associated with the administration of NSAIDS, coronary artery disease, diabetes, HD patients and cirrhosis[11]. It was also found that congestive heart failure, PD, diabetes and albumin were associated with peptic ulcers in ESRD patients[12].

Studies have shown that low dose PPIs are given as prophylactic agents for relieving gastric symptoms and ulcers. Prophylactic administration of omeprazole to dialysis patients effectively reduced the incidence of peptic ulcers[13]. This is first study, to our knowledge, suggesting pr effectiveness of PPI in preventing UGIB in dialysis patients as many studies have found an association between PPIs and bone metabolism[14], vascular calcification[15], and fractures[16]. As it's a retrospective study, so patients were not randomized. Many subjects in the PPI group showed gastric symptoms. The difference in sex, age, cardiovascular disease, smoking or diabetes between both groups was not significant. This study assessed mortality in both groups, while bone mineral density and vascular calcification were not assessed. In our study data concerning ambulatory status was not included.

There are several limitations of this study. First, general conclusions could not be drawn as it was not a randomized controlled study. However, it is difficult to conduct such a study in practice because of ethical considerations. Second, Helicobacter pylori was examined in a few patients only. Third, patients given H_2 receptor antagonists were excluded. It has been found that during the dual anti-platelet regime, H_2 receptor antagonists are the potential alternative of PPIs for preventing UGIB without more risk of

cardiovascular abnormalities. Finally, long term side effects of PPIs were not assessed as vascular calcification, mineral bone disease, serum magnesium and bone fractures were not considered.

CONCLUSION

It was found that in ESRD patient's risk of UGIB is more in control group as compared to PPI group. Moreover, PPI is considered effective and safe for preventing UGIB in dialysis patients and do not increase mortality. More large scale studies are required for confirming our results.

Author's Contribution:

Concept & Design of Study:	Poonum Khalid, Ghulam Abbas
Drafting:	Arslan Akbar Saeed, Poonum Khalid, Muhammad Muzammil
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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