Original Article

Proton Pump Inhibitors Induced Hypomagnesaemia in End Stage Renal Disease Patients

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ABSTRACT

Objective: To compare the severity of hypomagnesaemia in end stage renal disease patients on hemodialysis taking proton pump inhibitors and standard therapy after three months of treatment.

Study Design: Randomized Controlled Trial (RCT) study.

Place and Duration of Study: This study was conducted at the Department of Nephrology, Pakistan Institute of Medical Sciences, Islamabad from May to Aug 2017.

Materials and Methods: This study involved 100 patients of both genders aged 18 years and above with end stage renal disease on hemodialysis. Patients were randomly allocated in two treatment groups. Group-A received PPI along with standard therapy of hemodialysis while those in Group-B received standard therapy of hemodialysis. The frequency of hypomagnesemia (<1.3 mEq/l) after 3 months of treatment was noted and compared between the two groups.

Results: The mean age of the patients was 50.89±10.20 years. Male to female ratio was found 1.7:1. The average blood urea, plasma albumin, serum creatinine, serum sodium, serum potassium, serum phosphate and serum calcium were not significantly different between two groups with p-value >0.05. Serum magnesium level was the only significant variable between two groups. The mean serum magnesium level was significantly lower in patients on PPI (1.48±0.26) versus control group (1.6±0.22) with p-value <0.05. The frequency of hypomagnesemia was significantly higher in patients on proton pump inhibitors (28.0% vs. 10.0%; p <0.05).

Conclusion: Proton pump inhibitors were found to be associated with hypomagnesemia in patients with end stage renal disease on hemodialysis.

Key Words: End Stage Renal Disease, Hemodialysis, Proton Pump Inhibitors, Hypomagnesemia

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INTRODUCTION

Gastrointestinal symptoms are much common in CKD and ESRD patients than general population. 51% to 70.7% patients on hemodialysis experience upper gastrointestinal symptoms. There are many mechanisms which explain such a high prevalence of gastrointestinal problems in these patients.[1] Uremic toxins, effect of dialysis, drugs and life style are some main underlying causative conditions.[1]

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Patients with high urea level are prone to erosive gastritis, ulcerative esophagitis and duodenitis.[2] Recurrence of H. Pylori after eradication is also common in uremic patients.[3] GI symptoms like nausea, vomiting, indigestion, bloating, abdominal pain, gastro-esophageal reflux, diarrhea and constipation cause malnutrition and decrease quality of life.[4]

Magnesium (Mg) is an important cation required for a number of cellular functions.[5] It is required for many enzymatic reactions like synthesis of adenosine triphosphate (ATP), ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). It also takes part in cell permeability and neuromuscular excitability by regulating ion channels. It has role in cellular apoptosis and proliferation. It must be noted that both humoral immune and cellular immune responses have involvement of Mg.[6] In body 50 to 60% of total magnesium is stored in bones, about 40% is in muscles and only 1% is found in extracellular fluid.[7] Magnesium equilibrium is strongly maintained by absorption through intestine and renal excretion as well as its exchange with bone. Mg2+is absorbed passively through tight junctions between enterocytes and actively through the combined actions of transient receptor potential melastatin -6 and -7 (TRPM6/7)

channels, which are present in the apical membrane of enterocytes in the intestine.[8]

Proton-pump inhibitors (PPIs) are a widely used first line and evidence-based therapy for upper gastrointestinal disorders like dyspepsia, gastroesophageal reflux disease, peptic ulcer disease, upper GI bleeding and H Pylori associated disease.[9] PPIs inhibit active proton pumps in gastric parietal cells and inhibit HCl production.[9]

PPIs when taken short-term exhibits excellent safety profile and clinically applicable adverse effects are rare. However, PPI therapy leads to hypergastrinemia, parietal cell hypertrophy leading to rebound acid hypersecretion,[10] hypomegnesaemia,[11,12] clostredium difficile associated disease,[13] osteoporosis[14] and AKI.[15]

PPI-induced hypomagnesaemia is primarily due to impaired intestinal absorption. Studies suggest that passive paracellular magnesium absorption is intact, but active transport via TRPM6/7 channels is disrupted. Although the pathophysiology has not been completely understood but it appears that a PPIs cause a decrease in pH of 0.5 of intestine lumen which alters TRPM6/7channel affinity for magnesium.[16] Tamora et al. concluded that chronic use of PPIs can lead to severe hypomagnesaemia.[17] Perazella et al. confirmed the association between PPIs and hypomagnesaemia in patients hospitalized at tertiary care medical centers.[18] Alhosani et al. performed a study on 62 hemodialysis patients, which showed that 39% of patients had hypomagnesaemia. [19]

Hypomagnesaemia is having specific clinical manifestation as it may lead to neuromuscular disturbances e.g., tetany, seizures, arrhythmias, hypoparathyroidism, osteomalacia, osteoporosis as well as concurrent metabolic disorders e.g. hypocalcaemia and hypokalemia.[20]

It was noticed significantly by Kanbay et al. that in CKD patients, future outcomes can be predicted by serum Mg level. In HD and CKD patients mortality rate increases with lowering of serum Mg levels.[21] It has been reported by Sakaguchi et al.[22] recently that in HD patients, high rate of non-cardiovascular and cardiovascular mortality can be predicted by hypomagnesemia.

There is limited literation on PPI induced hypomagnesaemia, therefore we are taking up this study to know the severity of hypomagnesaemia in dialysis dependent patients using PPIs in our center to know the hypomagnesaemia burden in our population and to suggest alterations in medications to prevent serious morbidity and mortality.

MATERIALS AND METHODS

A randomized control study was conducted at department of Nephrology, Shaheed Zulfiqar Ali Bhutto Medical University PIMS Islamabad from May 2017 to August 2017. A study conducted by Alhosaini et al.[19] in 2014 reported the proportion of hypomagnesemia in PPI group 55.2% whereas in control group 24.2%. taking the result of the above said study from the literature keeping power of test 80%, and level of significance 5% the minimum sample size for our study was 40 in each group (Total sample size=80). We fixed the sample size 50 in each group, taking total sample size 100 who were fulfil the inclusion/exclusion criteria.

After approval from ethical committee. After detailed history and physical examination, a written consent was also taken from patients or guardians. Group-A patients were allowed to take a single dose of 40mg omeprazole in the morning on empty stomach. After 3 months of treatment all lab values were noted. The severity of hypomagnesaemia (serum magnesium level < 1.3 mEq/l) in two groups was also examined. The data was entered and analyzed through SPSS version 23.0. The p value <0.05 was considered as significant.

RESULTS

Out of 100 patients there were 63% male and 37% female. The age of the patients ranged from 30 years to 70 years was 50.89±10.2 years. Majority (33.0%) of the patients were aged between 51-60 years followed by 29% patients in the range of 41-50 years and 21% patients in the range of 61-70 years while only 17% patients were aged between 30-40 years. The age of patients was normally distributed as the p value of Kolmogorov Simonov test was >0.05. (Table 1)

Table No.1: Normality test through Kolmogorov Smirnov test of normality for qualitative variables of the study

Variable	Statistic	P value
Age in years	.06	>0.05
Serum Creatinine	.11	<0.05
Blood Urea	.14	<0.05
Serum Potassium	.13	<0.05
Serum Sodium	.28	<0.05
Serum Calcium	.08	>0.05
Serum Phosphate	.1	<0.05
Plasma Albumin	.12	<0.05
Serum Magnesium	.07	>0.05

Table No.2: Comparison of Non-Gaussian lab variables through Mann-Whitney U test between PPI and control groups

Variables	Mann Whitney U Statistic		P value
	PPI	Control	
Serum Creatinine	46.1	54.9	>0.05
Blood Urea	46.66	54.34	>0.05
Serum Potassium	49.18	51.82	>0.05
Serum Sodium	48.98	52.02	>0.05
Serum Phosphate	54.13	46.87	>0.05
Plasma Albumin	49.14	51.86	>0.05

We also test the normality of the lab variables from which serum creatinine, blood urea, serum sodium, serum potassium, serum phosphate and plasma albumin were not belong to normal distribution and was tested between groups with Mann-Whitney U test. The Mann-Whitney U test showed that the mean rank values of lab variables were not significantly different between two groups with p value >0.05. (Table 2).

Serum calcium and serum magnesium was the two lab variables which were belongs to normal distribution with p value >0.05. The independent sample t test showed that the mean serum calcium was not significantly different between two groups (with p value >0.05 whereas the mean serum magnesium was found the only lab variables which was significantly different between two groups with p value <0.05. (Table 3).

Table No.3: Comparison of Gaussian variables through independent sample t test between PPI and Control group

Variables	Mean ± Standard deviation		P value
	PPI	Control	
Age in years	50.62±10.01	51.16±10.49	>0.05
Serum Calcium	8.31±1.14	8.5902±1.32	>0.05
Serum Magnesium	1.48±0.26	1.6±0.22	<0.05

The frequency of hypomagnesemia was significantly higher in patients on proton pump inhibitors 28.0% versus 10.0% in control group with p value <0.05. (Table 4).

Variables	Categories	PPI	Control	P value
Gender	Male	36	27	>0.05
	Female	14	23	
Hypomag-nesemia	Yes	14	5	<0.05
	No	36	45	

Table No.5: Stratification the result with respect of gender and age groups

Variables	Categories	Hypoma-gnesemia	PPI	Control	P value
Gender	Male	Yes	8	4	>0.05*
		No	28	23	
	Female	Yes	6	1	<0.05**
		No	8	22	
Age groups	30-40	Yes	3	0	<0.05**
		No	6	8	
	41-50	Yes	5	3	>0.05**
		No	10	11	
	51-60	Yes	3	1	>0.05**
		No	14	15	
	61-70	Yes	3	1	>0.05**
		No	6	11	

*Chi square test **Likelihood ratio test

We also stratified the result to find the reason of significant difference of proportion of hypomagnesemia between two groups. The proportion of hypomagnesemia was not equal in female patients and in younger age patients (30 to 40 years of age) between two groups. (Table 5).

DISCUSSION

Patients of Chronic kidney disease (CKD) are prone to develop upper gastrointestinal (GI) symptoms and mostly show erosive gastritis, ulcerative esophagitis, and duodenitis on biopsy[23]. PPI's (proton pump inhibitors) are commonly used for the management of upper GI related problems. However, there are potential side effects particularly the risk of hypomagnesemia with long term use[24].

In the present study, the mean age of the patients was 50.89±10.2 years. Majority (33%) of the patients were aged between 51-60 years followed by 29% patients in the range of 41-50 years and 21% patients in the range of 61-70 years while only 17% patients were aged between 30-40 years. The patients of ESRD were generally reported to the age.[25-26]

There were 63 (63%) male and 37 (37%) female patients in the study. Many other also reported the same sex distribution which shows that there may be overall a high percentage of male patients as compare to female in ESRD.[27-30]

In the present study, the mean serum magnesium level was significantly lower in PPI group. This was also reported as same in many recent studies. Alhosaini et al.[19] previously reported similar significant difference in the mean serum magnesium level with and without PPI (1.37±0.1 vs. 1.7±0.2) mEq/l with p value <0.05. The same results were also observed in the study conducted in 2015 where the mean serum magnesium level among patients with and without PPI was 2.52±0.42 versus 2.68±0.46 mg/dl which was also non-significant at 5% level of significance.

We observed that the frequency of hypomagnesemia was significantly higher in patients treated with PPI. The proportion of hypomagnesemia was significantly high in PPI group with p value <0.05. The result of Gau et al.[31] and Kim et al[32] was strengthen our finding as in both studies reported significantly higher frequency of hypomagnesemia with PPI as compare to control group (23.2% vs. 10.7%; P <0.05) and (28.6% vs. 14.2%; P <0.05) respectively.

We also stratified our results to find out the reason behind this significance. The result showed that the proportion of hypomagnesemia was significantly higher in PPI group as compare to control group only in the patients having comparatively young age i.e. belong to (30 to 40 years of age) while in rest of the age groups the proportion of the hypomagnesemia was not statistically different including the age group (50-61 and 61-70 years) where the patients were generally belong to Similarly, we observed that the proportion of hypomagnesemia was higher only in female patients whereas we found that majority of the patients were

male. In the light of above stratified results it's recommended that few more trials should plan with more restrict inclusion criteria with respect of patient's age group and specifically for female.

CONCLUSION

Proton pump inhibitors were found to be associated with hypomagnesemia in patients with end stage renal disease on hemodialysis. Serum magnesium level should be monitored to enable timely identification and correction of hypomagnesemia to avoid complications.

Author's Contribution:

Concept & Design of Study:	Shakeel Khan
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Data Analysis:	Ahmad Shamim Khan, Adnan Akhtar, Asma Hafeez
Revisiting Critically:	Shakeel Khan, Usman Khalid
Final Approval of version:	Shakeel Khan

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

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