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Original Research Article

Association of Proton Pump Inhibitor Therapy with Hypomagnesemia: A Comparative Observational Study

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Conflict of interest: Nil

Abstract

Background and Objectives: Proton pump inhibitors (PPIs) are widely used in the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease, and other conditions associated with increased gastric acid secretion, as well as in the prevention of gastric ulcers in patients who require prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids. They are available both by prescription and over-the- counter (OTC) means, Present study was conducted to investigate whether there was a link between PPI dose or treatment duration and the development of hypomagnesemia.

Methods: The present study was an observational, cross-sectional study, conducted over a period of 2 years. Serum total magnesium levels was tested in inpatients who were on PPI for >30 days and normal outpatients as per inclusion and exclusion criteria. Primary outcome was hypomagnesemia , incidence of which was evaluated across magnesium levels that was categorized into hypomagnesemia (Mg <1.7 mg/dl) normomagnesemia (1.7 – 2.4mg/dl) hypermagnesemia (>2.4mg/dl) Qualitative variables were compared using Chi-Square test /Fisher's exact test. Correlation was done using Pearson or Spearman correlation based on normality of distribution

Results: Due to COVID 19 pandemic total only 90 patients presented to the inpatient and the outpatient department were enrolled against initial estimated sample size of 132 patients. Enrolled patients were divided into two groups (PPI users and non- users) in a 1:1 ratio for our primary endpoint. The average age of patients enrolled in the PPI and non-PPI groups was 55.84 ± 15.38 years and 55.06 ±16.72 years. The mean serum magnesium level among patients with PPI used ≤30days was 1.69 ± 0.21 mg/dl and those used >30 days was 1.68 ± 0.27 mg/dl.

Conclusion: Hypomagnesemia is not associated with prolong use of PPI in our study population. No significant difference was seen in the serum magnesium level among patients who used PPI ≤ 30 days or >30 days.

Keywords: Magnesium, Proton Pump Inhibitors, Hypomagnesemia.

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Introduction

Proton pump inhibitors (PPIs) are widely used in the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease, and other conditions associated with increased gastric acid secretion, as well as in the prevention of gastric ulcers in patients who require prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids [1].

They are available both by prescription and over-the- counter (OTC) means, and they are considered to be one of the most popular drugs sold worldwide, as well as one of the most prescribed in both primary and secondary care [2]. Despite the fact that the recommended treatment period for acute gastric and duodenal ulcers is 4 to 8 weeks the US Food and Drug Administration (FDA) recommends that no more than three 2-week treatment courses be provided per year[3].

According to the authors, this safety communication was developed after reviewing 38 cases from the Adverse Event Reporting System as well as 23 published case reports. Despite the fact that this information was included to the warnings and precautions sections of the labels for all PPIs, the FDA made this decision without consulting substantial observational or confirmatory studies to support it. It is possible that PPIs will produce hypomagnesemia by lowering intestinal magnesium absorption, which will result in decreased urine magnesium excretion [4,5].

Although many case reports have described patients with PPI-induced hypomagnesemia, the impact of PPI use on hypomagnesemia has not been fully clarified in comparative studies. In some studies, the association between PPI use and hypomagnesemia was not identified, while in others, PPI use was found to increase the risk of hypomagnesemia [6].

The discrepancy between these studies may be attributed to various patient characteristics, and/or underlying conditions. To provide an update on this topic, the present study was conducted to examine this question and explored whether there was an association between PPI dose or treatment duration and the development of hypomagnesemia.

Materials and Methodology

This was a single centric, observational, cross sectional, comparative study conducted in Department of General Medicine of a tertiary care hospital for a period of 2 years, from October 2019 to October 2021.

All patients attending medicine outpatient/inpatients department of our hospital**.** Purposive sampling was adopted to select the individuals for the study.

Sample Size Estimation: Based on study by Dunkin shah et al (7) it is observed that hypomagnesemia was seen in 13% of proton pump inhibitor users. Hence assessing P_1 = 13%, P_2= 1% with 95% confidence interval and 80% power sample size estimated for the study is 66 in each group

$$n = [Z(1\text{-alpha})+Z(1\text{-beta})]^2 xp1q1+p2q2/ (\text{difference})^2$$

1. **Group 1**: 66
2. **Group 2**: 66

Group 1: Patients on proton pump inhibitor therapy for more than 1 month. Group 2 Age, gender, comorbidities matched normal individuals

Ethical Considerations: The study was initiated after obtaining approval from the AJ institutional ethics committee and department of Medicine. A written informed consent was taken from the patients when they were stable and ready for enrolment into the study.

Inclusion criteria

Male or female patients in the age group of 18-80 years who had been on PPI therapy for a period of at least 1 month. Patients not taking PPI therapy belonging to similar morbid conditions. Patients willing for study. Patient who are medically fit and given informed written consent.

Exclusion Criteria: Pregnant or nursing women. Patients suffering from acute pancreatitis, diarrhea, congestive heart failure. Patients on ethacrynic acid, furosemide, gentamycin, amphotericin, B, cyclosporine, digitalis, cisplatin, antihypertensives like beta blockers, ACE inhibitors. Patients not willing to give consent for further investigations.

Study Procedure: The study was initiated after approval from Institutional ethics committee and department of general medicine. All the patients presenting to the medicine OPD/IPD and who meet the inclusion and exclusion criteria were part of the study. Written informed consent in the language understandable was obtained from patients or their legal representative whenever possible. All patients were subjected to full clinical examination including vital signs assessment such as heart rate, respiratory rate, blood pressure, temperature. Serum magnesium level was confirmed using standard test and was compared in both the group, this was done from the hospital-based biochemistry lab in all patients.

Statistical Analysis: Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality is rejected, then non-parametric tests were used. Descriptive statistics were analysed and presented in terms of mean with standard deviation. Qualitative variables were compared using Chi-Square test /Fisher's exact test. Correlation was done using Pearson or Spearman correlation based on normality of distribution. A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Result

Table 1: Age and Gender wise distribution of patients

Age (year)	PPI users	Non PPI user
<20	0	2
21-35	5	5
35-50	11	10
51-65	15	12
65-80	13	15
>80	1	1
Total	45	45
Average age	55.84 ± 15.38	55.06 ±16.72
P value	0.81 (Unpaired t test)	

Majority of patients in both the group were >50 years of age. The average age of patients enrolled in the PPI and non-PPI groups was 55.84 ± 15.38 years and 55.06 ±16.72 years, respectively. No significant difference (p=0.81) was seen in the age wise distribution of patients. Male predominance was seen among patients in both the group. No significant difference (p=0.66) was seen in the gender distribution of patients.

Table 2: Serum Magnesium comparison

Serum Magnesium (mg/dL)	PPI users	Non PPI user	P value
<1.7	25	22	0.67 (Fisher test)
1.7 to 2.2	20	22	0.83 (Fisher test)
>2.2	0	1	1.00 (Fisher test)
Mean	1.68 ± 0.25	1.71 ± 0.25	0.54 (Unpaired t test)

Majority of patients in PPI user group had serum magnesium level <1.7 mg/dl where as those in the nonPPI user group had serum Mg level between 1.7 to 2.2. The average serum magnesium level among PPI users was 1.68 ± 0.25 mg/dL, while in non-PPI users was 1.71±0.25 mg/dl. The was no significant difference (p=0.54) between the two groups.

Table 3: Correlation of days of PPI use and serum magnesium

	Days of PPI use and Serum Magnesium
Correlation coefficient (Pearson Correlation)	-0.17 (-0.44 to 0.12)
P value	0.24

Serum magnesium was negatively correlated with days of PPI use in our study population. The correlation was not statistically significant.

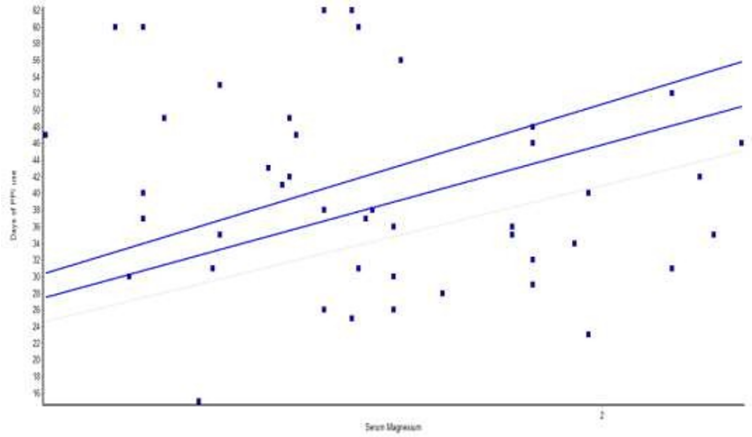

Figure 1: Correlation of days of PPI use and serum magnesium

Table 4: Days of PPI used and serum Magnesium level

Days	No of patients	Serum Magnesium (mg/dL)
≤ 30	10	1.69 ± 0.21
>30	35	1.68 ± 0.27
P value	0.90 Unpaired t test)	

The mean serum magnesium level among patients with PPI used ≤ 30days was 1.69 ± 0.21 mg/dl and those used >30 days was 1.68 ± 0.27 mg/dl. NO significant difference was seen in the serum magnesium level among patients who used PPI ≤ 30 days or >30 days.

Discussion

Proton pump inhibitors (PPIs) are widely used to treat gastroesophageal reflux disease, peptic ulcer disease, and other conditions associated with increased gastric acid secretion, as well as to prevent gastric ulcers in patients who require long-term use of nonsteroidal anti-inflammatory drugs or corticosteroids.

The baseline demographic characteristics of patients enrolled in the study revealed that the average age of patients enrolled in the PPI and non-PPI groups was 55.84 ±15.38 years and 55.06 ±16.72 years, respectively, with no significant difference (p=0.81). Both groups had a relative male predominance, but there was no significant difference in the gender distribution of cases (p=0.66). PPI utilisation was evaluated in an Indian study conducted by Shabbir Pendhari [8], who reported that the average age of PPI utilisation was 47.55±16.16 years, with males constituting 54.43 % of the cohort. Another study from South India [9]

found similar results, with an average age of 49 ±16.23 years and males accounting for nearly 82 % of the study population.

PPI users had an average serum magnesium level of 1.68 ± 0.25 mg/dL, while non- PPI users had an average of 1.71±0.25 mg/dL; there was no significant difference (p=0.54) between the two groups. In PPI users group, hypomagnesemia (<1.7 mg/dL) was found in 25 (55.55 %), while in non-users, it was found in 22 (48.88 %).

Similarly, Monica Chowdhry [10] in her study found that mean Mg levels were normal in PPI users (1.84 ± 29 mg/dL) and PPI nonusers (1.85 ± 30 mg/dL). In both groups, the prevalence of hypomagnesemia was 14.7 % vs. 15.1 %, with a P value of 0.77, respectively. Similar to hypomagnesemia, the prevalence of severe hypomagnesemia (<1.0 mg/dL) was not statistically different between the two groups (0.83% vs. 0.42%). A few more recent studies, albeit of smaller scope, have found no link between PPIs and hypomagnesemia as well [11,12]. In a rare prospective study conducted after 12 months of PPI use, researchers found stable Mg levels [12]. In a meta analysis conducted by Thawin Srinutta [6], hypomagnesemia was found in 19.4 % of PPI users compared to 13.5 % of nonusers in 16 observational studies, including 13 cross-sectional studies, 2 case-control studies, and 1 cohort study.

In a meta-analysis, PPI use was found to be significantly associated with hypomagnesemia, with an OR of 1.83. Our study had a few limitations; because it was a single centric study conducted in a small percentage of people in south India, the findings may not be representative of the entire country; therefore, we recommend conducting a large scale multicentric study involving people from various regions of the country; this will provide better, more robust data that can be trusted. Long-term outcomes or complications could not be tracked due to the study's design.

Conclusion

The mean serum magnesium level among patients with PPI used ≤ 30days was 1.69 ± 0.21 mg/dl and those used >30 days was 1.68 ± 0.27 mg/dl. The average serum magnesium level among PPI users was 1.68 ± 0.25 mg/dL, while in non-PPI users was 1.71±0.25 mg/dl, without any significant difference (p=0.54). Hypomagnesemia was not associated with prolong use of PPI in our study population.

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