Original Article

Correlation of Long Term Proton Pump Inhibitors (PPI) Use with Iron and Vitamin B12 Deficiency Anaemia

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Abstract:

The Suppression of gastric acid by long term use of PPI may decrease iron and vitamin B12 absorption and might be causing iron and vitamin B12 deficiency anaemia. This comparative cross-sectional study was conducted among patients with peptic ulcer disease from November 2017 to March 2020; attending in the Internal Medicine department of Bangabandhu Sheikh Mujib Medical University (BSMMU). A total of 80 patients were included and divided into group-A (PPIs user) and group-B (non-PPI user), each group containing 40 patients each. The group-A included patients who were taking PPIs for more than one year and aged from 18 to 70 years and group-B the control group who were not taking PPIs for atleast 1(one) year. The data were analysed by Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). The study shown that male were 18(45%) and 19(47.5%) in group A and B respectively and female were 22(55%) and 21(52.5%) in group A and B respectively. The mean age of male and female was (year) 45.35 ± 12.46, 44.85 ± 15.24, respectively. Most of the patient took omeprazole 62.5% follwed by, esomeprazole 20%, pantoprazole 12.5%, rabeprazole 5%. About 47.5% of the patient took PPI for more than 2 years, and 52.5% took between 1-2 years. The mean (±SD) haemoglobin (Hb) level was 10.93±2.00 g/dl amongst group-A and 13.16±1.68g/dl in group-B, the difference is statistically significant (P<0.001). The mean serum iron of the PPI users (group-A) was 46.43±22.79, and of non-PPI users (group-B) was 84.95±33.18, the difference between iron level between two groupd was satistically significant (odds ratio -6.38 ; CI-2.28-17.84 and P-value <0.001). The PPI user group, mean vitamin B12 was 449±166.99 and in non-PPI group it was 432.85±175.93, which was statistically nonsignificant (P-value -1.00). Amonst all the participant low serum concentrations of iron, ferritin and transferrin were found 23(57.5%), 18(45%) and 27(67.5%), respectively in Group-A (PPI user group) and 7(17.5%), 7(17.5%) and 8(20%) respectively in Group-B (PPI-non user). The difference was statistically significant (p<0.05) between the two groups. But the value of TIBC was found to be high in 36 (90.0%) participants in both groups, which was statistically non-significant(p=0.33). Hematocrit (HCT) were low in 35 (87.5%) participants in Group-A and 25(62.5%) in Group-B. The difference was statistically significant (p<0.05). Low MCV was found in 10(25%) in the PPI user group and 4(10%) in the non-user group, whish was statistically non-significant. No significant differences in vitamin B12 concentrations (pg/ml) 449±166.99 vs 432.85±175.93 were found between groups A and group B, respectively. There was a weak negative Pearson's correlation shown in ascatter diagram between duration of PPI use, and the iron level of group A (n=40) (r=-.311, p=.051). A negligible Pearson's correlation was seen in the scatter diagram between the duration of PPI use, and vitamin B12 level of group A (r=+.05 p=.977). This study showed a significant decrease in haemoglobin, haematocrit, iron, ferritin, transferrin saturation in participants taking PPIs for more than one year, compared with age and gender-matched controls. No significant change of MCV, TIBC (Total Iron Binding Capacity) and vitamin B12 were noticed between groups. In conclusion, the study found a significant decrease in hematologic indices and iron profile among patients receiving PPIs for longer than one year. There was no substantial change of Vitamin B12 levels was detected between long-term PPIs users and non PPIs user groups. So, from the study it is suggested that judicial prescription of long-term PPIs must be practiced. However, the small sample size and short study duration were the limitation of the study.

Keywords: *Proton Pump Inhibitors, iron deficiency anaemia, vitamin B12 deficiency anaemia.*

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INTRODUCTION

Anaemia has long been recognized as a significant global health problem affecting a considerable proportion of the world's population. Iron deficiency is thought to be the most common cause of anaemia, but other nutritional deficiencies like vitamin B12 can cause anaemia.[1] The anaemia is defined as a fall of haemoglobin concentration below a statistically defined threshold lying at two standard deviations below the median of a healthy population of the same age, sex, and stage of pregnancy.[2] According to world health organization(WHO), about 500 million to 1(one) billion individuals representing 15-20% of the world population are presently affected by nutritional anaemia, and half of these have iron deficiency.[3] Nutrition survey of rural Bangladesh during 1975-76 reveals that about 70% of the Bangladeshi population suffers from anaemia with a

mean haemoglobin value of 9.7 gm/dl. The data on the aetiology of anaemia reveal that iron deficiency may be a substantial cause of anaemia in the Bangladeshi population.[1] While epidemiological findings indicate the enormous extent of the problem globally, the developing countries are the most affected areas. It remains a significant problem with serious public health, social and economic consequences and undermines human potential. The prevalence of anaemia in developing countries is predictably three to four times higher than in industrialized countries.

Since their advent in the late 1980s, proton pump inhibitors (PPIs) have become widely used to treat many upper gastrointestinal disorders, including gastro-esophageal reflux disease, peptic ulcer disease, and stress ulcer prophylaxis. The use of proton pump inhibitors (PPIs) in treating gastrointestinal diseases has evolved over recent years. Initially intended for short-term use, PPIs are increasingly being used, often inappropriately, as long-term maintenance medications. Overutilization of PPIs is also well documented. [4] In one series of hospitalized patients, rates of PPI use increased six-fold from admission to discharge, presumably because of failure to discontinue PPIs started for stress ulcer prophylaxis. The absorption rate of non-heme iron is extremely poor without gastric acid. It has long been known that iron absorption is poor under conditions of gastric acid deficiency, such as that observed in patients with atrophic gastritis.[5] Gastric acid plays a vital role in iron and vitamin B12 absorption; the long-term use of PPIs suppresses gastric acid production and has been shown to increase the risk of vitamin B12 deficiency.[6] The study's objective was to explore the association of long-term proton pump inhibitor use with iron and vitaminB12 deficiency anaemia.

MATERIALS AND METHOD

This was a comparative cross-sectional study oconducted among 80 patients of peptic ulcer (PUD), where 50% of them were taking PPIs (Proton Pump Inhibitor) for more than one year, at least 20 or more per month ageing from 18 to 70 years and rest were using medication other them PPIs attended inpatient or outpatient Department of Internal Medicine at Bangabandhu Sheikh Mujib Medical University from November 2017 to March 2020. The patients consented to study participation and were recruited at the first visit. Data collection was accomplished by maintaining adequate privacy and confidentiality without any physical harm abiding by the Helsinki declaration. Patient with gastrointestinal bleeding, excessive menstrual bleeding, strict vegetarian, known case of chronic kidney disease and dialysis, chronic liver disease, smoking, pregnancy, history of intestinal surgery, malabsorption, malignancy, connective tissue disease, the patient receiving drugs like prolonged ecosprin, NSAIDs, erythropoietin, vitamins, iron or folic acid preparations anticoagulation with coumarin or low-molecular-weight heparin, antiepileptics users, bleeding disorders were excluded from the study.

This study was done in two groups involving group A and group B. Patients who received PPIs for at least one year were enrolled as group A. Age and sex-matched controls were identified using the same inclusion and exclusion criteria as group B. The primary exposure of interest was PPIs use for more than one year. Duration and dose of medication and medication changes were recorded and tabulated after at least one year of PPI therapy. Data collection sheet was filled up from comprehensive history, including deworming, medical records, physical findings, and laboratory reports. Dates of laboratory results were recorded to assess the length of time between collection and initiation of PPIs therapy.

Biochemical assay:

Hematologic indices (including haemoglobin, hematocrit, red blood cell count, mean corpuscular volume, white blood cell count, and platelet count) were measured using Automated Haematology Analyzer Pentra ABX-120DX. Additional laboratory data, including iron, TIBC, Serum Ferritin, vitamin B12, were measured using the ARCHITECT Plus *ci*4100 autoanalyzer manufactured by Abbott, Ilinois, USA.

Cut-off values:

The cut-off values for anemia, in male: haemoglobin level<13 mg/dl, female: haemoglobin level<12 mg/dl (WHO, 2011). Baseline reference ranges for s.iron male 55-160 µg /dl, Female 40-155 µg/dl (Gomella, 2007). Baseline reference ranges for s.ferritin male 30-200 ng/L and female 30-150 ng/L (Isanaka et al., 2012). The level of total iron-binding capacity (TIBC) of serum 155-300µg/dl and serum vitamin B12 is considered 239-931 pg/ml pg/ml according to BSMMU Biochemistry Lab using the ARCHITECT Plus ci4100 autoanalyzer manufactured by Abbott, Ilinois, USA.

Statistical analysis:

The numerical data obtained from the study were analyzed, and the significance of differences was estimated by using statistical methods. Continuous variables were expressed as mean values ± standard deviation and compared using Student's t-test. Categorical variables were expressed as frequencies with percentages and compared using the Chi-square test or Fisher's exact test when & where appropriate. P values less than 0.05 were considered

statistically significant. Data were compiled and analyzed using SPSS version 20.0(SPSS Inc., Chicago, IL, USA).

RESULT

Table- I shows a total of 80 participants were selected for this study. The participants were divided into groups; each group included 40 participants, Group-A who received PPIs (patients who have a history of taking PPIs for at least one year) such as esomeprazole, omeprazole, pantoprazole, and rabeprazole) either single or in combination and Group B (control, PPI non-users). Amongst the participants, male were 18(45%) & 19(47.5%) in group A & B respectively, female were 22(55%) & 21(52.5%) in group A & B respectively. Mean age(year) of male & female were 45.35 ± 12.46, 44.85 ± 15.24 respectively. The average BMI(Kg/m^2) in groups A & B were 23.55 ± 4.45, 22.15± 3.63, respectively

Table I: Demographic characteristics of the participant of Group-A and Group -B (N=80)

Characteristics	Group A (n = 40) Frequency n (%) Mean±SD	Group B (n = 40) Frequency n (%) Mean±SD	P-value
Age(year)	45.35 ± 12.46	44.85 ± 15.24	0.873
Male	18 (45%)	19 (47.5%)	0.81
Female	22 (55%)	21 (52.5%)	
BMI (Kg/m^2)	23.55 ± 4.45	22.15± 3.63	0.80

Data are expressed as frequency and percentage,
Independent-Samples T-Test is done for quantitative data,
Chi-square test is done for qualitative data

Table-II shows most of the patient (62.5%) took Omeprazole follwed by, Esomeprazole 20%, Pantoprazole 12.5%, Rabeprazole 5%. Among PPI users, 47.5% of patients took PPI more than 2 years, and 52.5 % took PPI between 1-2 years

Table - II: Distribution by categories & duration of Proton pump inhibitor (PPI) use (N=40)

PPI generics & duration	Frequency (N)	Percentage
Omeprazole	25	62.5
Esomeprazole	08	20
Pantoprazole	05	12.5
Rabeprazole	02	05
1 to 2 year	21	52.5
More than 2 year	19	47.5

Table- III shows in this study ,the mean haemoglobin level was 10.93±2.00 in group-A and 13.16±1.68 in group-B , which is statistically significant (OR [Male 8.38 (1.77-39.7) & Female 4.33 (1.19-15.69)] & P-value< 0.001). There was significant difference of haematocrit (HCT) level between the two groups(HCT level was 34.84±6.33 vs 41.04±5.62 in group-A vs group-B, respectively, OR -4.2(1.35-13.06),p-value <0.001). The mean corpuscular volume (MCV) was 84.92±10.11 vs 88.31±6.15 in group-A and group-B, respectively(OR 3 :0.85-10.54 & p-value-0.074). The study has also shown a significant difference between groups in term of concentration of serum iron (46.43±22.79 vs 84.95± 33.18 in group-A vs group-B, OR-6.38 (2.28-17.84), P-VALUE <0.001) ; in serum ferritin level (45.64±37.99 vs 90.13±66.51 in group-A vs group-B, OR-6.38 (2.28-17.84), P-VALUE<0.001) and transferrin saturation (12.96±6.95 vs 24.63.±8.88 in group-A vs group-B, OR-8.31 (3-23.01),p-value<0.001). But, there was no significant difference in between two groups for total iron binding capacity(TIBC) (357.18.±59.37 vs 345.33±48.31 in group-A vs group-B, OR- 1 (0.23-4.31),P-value-0.331), and for vitamin B12 concentration(449±166.99, vs 432.85±175.93, in group-A vs group-B, OR- 1 (0.13-7.47) p value-0.675)

Table III: Comparison of hematologic indices, iron profile and vitamin B12 between two groups (N=80)

Variables	Group A (n=40) Mean±SD	Group B (n=40) Mean±SD	Odds Ratio (CI)	P-value
Hb (g/dL)	10.93±2.00	13.16±1.68	Male 8.38 (1.77-39.7) Female 4.33 (1.19-15.69)	<0.001
HCT %	34.84±6.33	41.04±5.62	4.2(1.35-13.06)	<0.001
MCV (fL)	84.92±10.11	88.31±6.15	3 (0.85-10.54)	0.074
Iron (µg/dL)	46.43±22.79	84.95±33.18	6.38 (2.28-17.84)	<0.001
Ferritin (ngm/L)	45.64±37.99	90.13±66.51	3.86 (1.38-10.76)	<0.001
TIBC (µg/dL)	357.18.±59.37	345.33±48.31	1 (0.23-4.31)	0.331
Tsat %	12.96±6.95	24.63.±8.88	8.31 (3-23.01)	<0.001
Vit B12 (pg/ml)	449 ±166.99	432.85±175.93	1 (0.13-7.47)	0.675

Data were expressed as mean±SD; P-value reached from chi-square test

Table- IV Shows among all the participant ,low serum concentrations of iron, ferritin and transferrin were found 23(57.5%), 18(45%) and 27(67.5%), respectively in PPI Group-A and 7(17.5%), 7(17.5%) and 8(20%) respectively in Group-B.The difference was statistically significant (p<0.05) between the two groups. But the value of TIBC was found to be increased in 36 (90.0%) participants in both groups, which was statistically non-significant

Table- V Shows the HCT concentrations were low in participants in both Group-A (87.5%) & in Group-B (62.5%) (OR:4.2(1.35-13.06;p value-0.010). The difference was statistically significant (p<0.05). Low MCV was found in 10(25%) in the PPI user group and 4(10%) in the non-user group, which is statistically not significant(OR:3 (0.85-10.54; p value-0.115). There was no significant differences in vitamin B12 concentrations (pg/ml) in between two groups (449 ±166.99 vs 432.85±175.93 in group-A vs group-B, respectively,OR: 1 (0.13-7.47;p value-1.00)

Table IV: Comparison of iron profile status between GroupA and Group B (N=80)

Variables		Group A (n=40)	Group B (n=40)	Odd ratio(CI)	P value
Serum iron concentration (µ/dl)	<50	23(57.5%)	7 (17.5%)	6.38 (2.28-17.84)	<0.001
	50-150	17(42.5%)	33 (82.5%)		
S. Ferritin (ng/mL)	<30	18(45.0%)	7 (17.5%)	3.86 (1.38-10.76)	<0.001
	30-200	22(55.0%)	33 (82.5%)		
S. TIBC (µ/dl)	150-300	4 (10.0%)	4 (10.0%)	1 (0.23-4.31)	0.331
	>300	36(90.0%	36 (90%)		
S. Transferrin saturation (%)	<16	27(67.5%)	8 (20%)	8.31(3-23.01)	<0.001
	>16	13(32.5%)	32 (80%)		

P-value reached from chi-square test

Table V: Comparison of haematocrit(HCT), mean corpuscular volume(MCV) and Vitamin B12 between Group A and Group B (n=80)

Variables		Group A (n=40)	Group B (n=40)	Odd ratio(CI)	P value
HCT %	<45	35 (87.5%)	25 (62.5%)	4.2(1.35-13.06)	.010
	>45	5 (12.5%)	15 (37.5%)		
MCV (fl)	<80	10 (25.0%)	4 (10.0%)	3 (0.85-10.54)	0.115
	>80	30 (75.0%)	36 (90%)		
Vitamin B12 (pgm/ml)	<230	2 (5.0%)	2 (5.0%)	1 (0.13-7.47)	1.00
	>230	38 (95.0%)	38 (95.0%)		

P-value reached from chi-square test

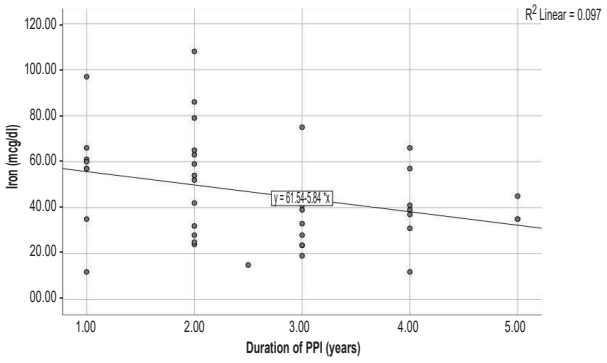

Figure 1A: Scatter diagram showing duration of PPI use and iron level of group A (n=40) has weak negative Pearson's correlation (r=-.311, p=.051)

There was a weak negative Pearson's correlation shown in a scatter diagram between duration of PPI use, and the iron level of group A (n=40) has (r=-.311, p=.051) (Figure- 1A).

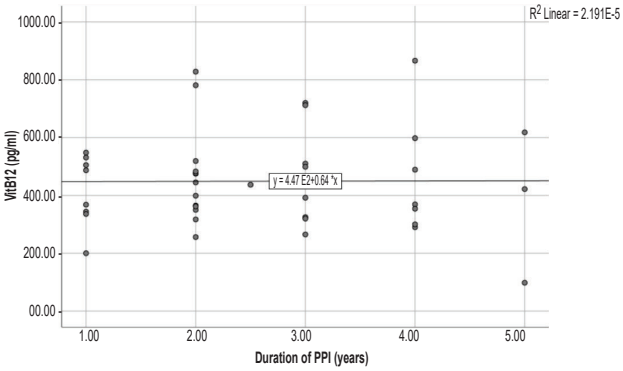

Figure 1B: Scatter diagram showing duration of PPI use and vitamin B12 level of group A (n=40) has negligible Pearson's correlation (r=+.05 p=.977)

A negligible Pearson's correlation was seen in the scatter diagram between the duration of PPI use, and vitamin B12 level of group A (n=40) has (r=+.05 p=.977) (Figure- 1B).

DISCUSSION

This comparative cross-sectional study was conducted in the Department of Internal Medicine in Bangabandhu Sheikh Mujib Medical University to observe the effects of long-term use of PPIs on haematological indices, iron profile, and vitamin B12. About Forty participants with a history of taking PPI for at least one year (including esomeprazole, omeprazole pantoprazole, rabeprazole were included in group-A and a forty participant of age and gender-matched controls were included in group-B. This present study observed that the mean age of the PPI user group was 45.35±12.46 years, ranging from 19 to 70 years, and non-PPI users were was 44.85±15.23 years, ranging from 18 to 70 years. Analysis revealed that difference between the two groups was not statistically significant (p>0.05). The mean age of the current study was very similar to a cross-sectional study done in California.[7]

This study observed that 45% of male and 55% of the female participants belonged to the PPI user group. In the non-PPI user group, 47.5% were male, and 52.5% were female. The difference was statistically not significant between the two groups. A study done by Lam, Schneider, Zhao, and Douglas (2013) found almost similar results in their study.[8]

There was no significant difference in the mean BMI between group-A and group-B (P= 0.80). Den Elzen and his colleagues conducted a study in 2008, and their finding was similar to this study.[9]

In this study, it was observed that among PPI-users, 62.5% used omeprazole, 20% used esomeprazole, 12.5% used pantoprazole, 5% used rabeprazole. A retrospective cohort study conducted by Sarazynski et al.(2011) found similar findings.[10] Roy and his colleagues conducted a study in 2016, and their conclusion is similar to this study .[11] In this present study, it was observed that among the PPIs user group, 52.5% of the participants used PPI for 1 to 2 years, and 47.5% used for more than two years.

The mean Hb was 10.9±2.00g/dl among PPIs users, and mean Hb was 13.16±1.68g/dl in PPIs non-user, which was significantly lower in PPIs user group A (P<0.001), which was consistent with a study done by Krieg et al.[12] Among the male PPI users, 11 subjects (61.1%) had a haemoglobin <13 g/dL who used PPIs for more than a year. The odds ratio (OR) for a <13 g/dl decrease was 8.38 (95% CI, 1.77–39.7). The study conducted by Shikita and her colleagues found the mean haemoglobin level in the PPIs user group was lower than the mean haemoglobin level in the PPIs non-user group.[13] This present study observed that 16 subjects (72.7)% of female PPIs users had a haemoglobin <12 g/dL while on PPIs for more than a year. The odds ratio (OR) for a <12 g/dl decrease was 4.33 (95% CI, 1.19–15.69), had 4.33 times significantly increased chance to develop anaemia in the PPIs user group compared to the non-user group. The study conducted by Sarazansky and associates shown a significant decrease in both haemoglobin and hematocrit in patients taking PPIs for more than one year which is consistent with this study.[10] Lam et al. (2017) showed that PPIs taken for longer than two years were associated with iron deficiency.[7] There was no decrease in the body iron stores or iron deficiency was observed in patients with Zollinger-Ellison syndrome who received continuous omeprazole therapy for up to 12.5 years.[14] There was a strong negative Pearson's correlation of Hb (r=-.729), moderate negative Pearson's correlation of hematocrit (r=-.67), weak negative Pearson's correlation (-.318) of transferrin saturation was found with the duration of long term PPI use. The risk of iron deficiency increased with more prolonged use of PPIs, with over four-fold increased risk among PPI users who took >1.5 pills/d for at least 10years.[7]

In this study, the PPI user group,the mean vitamin B12 was 449 ±166.99, mean vitamin B12 was 432.85±175.93 in the non-PPI user group which was statistically not significant. A similar observation was found in a study done by DenElzenet al. (2008), where they showed that there were no differences in mean serum levels of vitamin B12 between the long-term PPI users and PPI non-user groups and the prevalence of vitamin B12 deficiency (serum level <150 pM) was similar in both the groups: four (3%)in PPI users and three (2%) in non-PPI user group which were consistent with our study. Valuck et al. (2004) found that the current use of PPIs for 12 or more months was associated with vitamin B12 deficiency.[15] Two studies conducted by Ter Helde et al. (2001) and Toliaet et al.(2008) in children reported there was no association between PPI use and vitamin B12 deficiency like the current study.[16,17]

CONCLUSIONS

PPIs have long been used to improve gastrointestinal disorders; however, the risks of the long-term use of these drugs have recently been taken into account. There was a significant decrease in hematologic indices and iron profile among patients receiving PPIs for longer than one year. No substantial change of Vitamin B12 levels was observed between long-term PPIs users and non PPIs user groups. We recommend that judicial prescription of long-term PPIs should be made; otherwise, it may cause iron deficiency anaemia. However, the sample size was small; the study was done for a limited period of time & it was a

single center study; hence it may not represent the whole community population. The systemic diseae were excluded clinically and specific investigation was not done . Most of the participants did not show documentation of taking PPIs, so there was a chance of recall bias. Further study should be undertaken with a larger sample size & in multiple centres to find out the real picture .

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Ethical Issue:
The Institutional Review Board of Bangabandhu Sheikh Mujib Medical University approved the protocol for this study.

Conflict of Interest:
The authors declare no conflict of interest.

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