ORIGINAL ARTICLE

# Platelet Count in Gastroesophageal Reflux Disease Subjects Using Proton Pump Inhibitors for Long Duration

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## ABSTRACT

**Objective:** Analyze the blood Platelet count in Gastroesophageal reflux disease patients consuming Proton Pump Inhibitors for long duration.

**Methods:** This was a case control study, conducted at Isra University Hospital, Hyderabad from Jan: 2016 to Sept: 2017. 100 cases and 100 controls were selected by convenient sampling through inclusion and exclusion criteria. 3ml blood sample was collected into EDTA tubes for complete blood counts. Age, gender, hematocrit, hemoglobin, erythrocyte, leukocyte and Platelets counts were noted. Data analyzed on statistical software SPSS (ver 21.0) at 95% Confidence interval ($P \leq 0.05$).

**Results:** Platelet count in cases and controls were $301.6 \pm 56.7 \times 10^6 \times 10^9/\mu L$ and $457.15 \pm 19.3 /\mu L$ ($P=0.0001$). Thrombocytopenia was observed in 13% cases compared to 3% control only ($P=0.0001$).

**Conclusion:** The thrombocytopenia may occur in those using Proton pump inhibitor for long duration.


**Key Words:** Gastroesophageal Reflux Disease, Proton Pump Inhibitors, Platelets, Hematocrit.

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## INTRODUCTION:

Proton pump inhibitors (PPIs) are widely prescribed acid lowering drug of clinical significance. PPIs are inhibitors of acid production by gastric parietal cells. Acid lowering occurs through the inhibition of proton pump ($H^+$- $K^+$ ATPase); located in the luminal border of gastric parietal cells. PPIs are widely used drugs since late 1980s. PPIs are potent inhibitors of acid secretion. The therapeutic role in acid peptic disease and gastroesophageal reflux disease is well established[1,2]. It is also used for the eradication of Helicobacter pylori infection that infects the gastric mucosa and is well established cause of acid peptic disease beside many others. Bleeding esophageal varices, esophageal strictures, Zollinger-Ellison syndrome and the maintenance therapy for Barrett's esophagus are few other conditions being treated by PPIs[3,4]. Omeprazole was the first PPIs prescribed for gastric problems[5]. Since then many varieties of PPIs salts are available. Their clinical effectiveness is nearly similar but differs as regards the pharmacokinetic profile, pharmacokinetics, bioavailability, posology and route of excretion[6]. Clinical safety of PPIs is matchless but previous studies[6,7] have shown serious concerns over their long term consumption. Many cases reports of adverse sequelie of long-term PPI consumption have been published. Infections by Clostridia difficile and associated- pseudo membranous colitis, lung pneumonia infections, intestinal bacterial growth and malabsorption do occur. Deficiencies of vital nutrients as vitamin B12, iron and magnesium also occur. Major concern of osteoporosis and bone fractures has been highlighted in the medical literature. Drug induced interstitial nephritis has been reported. Chronic atrophic gastritis causes mal-digestion and


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malabsorption[7,8]. Food and Drug Administration (FDA) has issued safety concerns regarding PPIs long term consumption and occurrence of osteoporosis, C. difficile infections and serum Mg++ deficiency. It is highly disappointing that none of gastroenterologist societies have recommended surveillance over adverse risks of PPIs use for long durations. The American Gastroenterological Association (AGA) could not recommend surveillance mainly because of insufficient evidence of PPIs adverse effects[7]. Risk of adverse reactions is rare with short term PPs use. A retrospective study and many case reports have reported PPIs induced thrombocytopenia[6,7], however, another retrospective study reported contrary results[8]. As the PPIs are widely prescribed agent in Pakistan hence it is worth to revisit adverse effects particularly in long term PPIs users. The present study prospectively analyzed the hematological finding particularly the blood platelet counts in long term users of PPIs. The present study will help the clinicians beware of adverse reactions in those using PPIs for long duration.

## METHODS

The present case control study took place at a tertiary care hospital of Isra University Hospital, Hyderabad from January 2016 to September 2017. A sample of 100 cases and 100 controls was calculated by 'sampling for proportions'. Cases were selected by convenient sampling. Diagnosed cases of Gastroesophageal reflux disease (GERD) using PPIs for >3 years duration was defined as a `case`. Age and gender matched subjects not using PPIs were defined as `control`. Cases were selected as per inclusion criteria. A subjects was included who met the criteria of; diagnosed GERD patients, using PPIs for >3 years duration, Dose of ≤ 40 mg PPIs per day, age 40 - 50 years, male and female gender. Cases exclusion criteria were; chronic liver disease, malabsorption, malnourished, malabsorption syndrome, diabetic subjects, history of multivitamin pill, meat and liver intake in last three months. Outpatient department and admitted subjects were evaluated to fulfill the inclusion criteria by patient history. Duration of PPIs of > 3months were confirmed and re-confirmed by medical officer and consultant physician respectively. Detailed drug and diet history was taken. GERD subjects fulfilling the inclusion criteria were asked of their willingness for study purpose. Willing volunteers were asked to sign the consent form after study protocol was explained by researcher. It was informed that laboratory expenses will not be paid by patients. All findings were noted in a pre-structured proforma. Confidentially of participants data was secured by researcher. Blood sampling was performed as per standard of sterilization conditions. Area was cleansed with alcohol swab. A tourniquet was fastened for making the vein prominent. 3 ml blood was taken into disposable syringe (BD, USA), poured into EDTA bottles for complete blood counts. Blood sample was run on a fully automated Sysmex KX-21 hematology analyzer. Results were collected. Hematocrit, hemoglobin, erythrocyte, leukocyte and Platelets counts were noted. Platelet counts were double checked by microscopic examination of blood smear slides. Normal Platelet counts were 1, 50, 000 4, 50,000 per μL. Thrombocytopenia was defined as Platelet counts <1, 00,000 per μL[10]. Data noted in proforma was typed in Excel sheet. A sheet of statistical software SPSS (ver 21.0) was opened as new and data was copied. Continuous and categorical variables were analyzed by Student t-test and Chi-square test respectively. Data analysis was performed at 95% Confidence interval ($P \leq 0.05$).

## RESULTS

Mean± SD age in cases and controls was found 51.5±9.19 and 50.3±10.59 years respectively (P=0.93). Male and female gender comprised 51% vs. 53% and 49% vs. 47% in cases and control respectively (P=0.91). Cases (PPI) revealed significant decrease in hematocrit, hemoglobin, erythrocyte and leukocyte counts compared to control (P<0.05). Platelet count in cases and controls were 301.6±56.7 $x10^6$ $x10^9$/μL and 457.15 ±19.3 /μL (P=0.0001) (Table-I). Normal Platelet counts in cases and controls were 87% vs. 97% respectively. Thrombocytopenia was

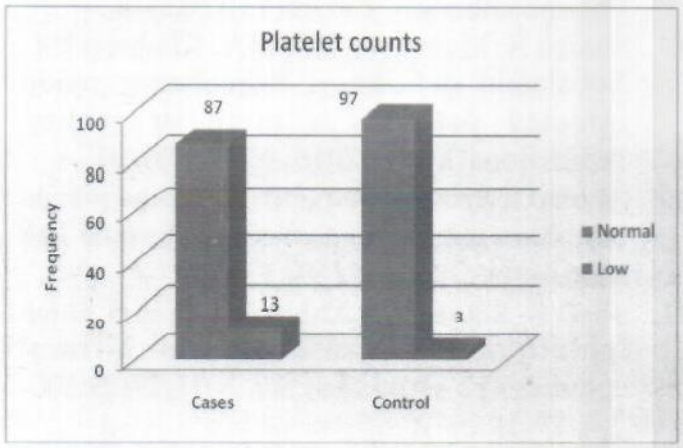
observed in 13% cases compared to 3% controls (P=0.0001) (Table-II, Graph-1).

**Table-I: Demographic & Laboratory Findings of Study Subjects**

| Variables | Cases | Controls | P-Value |
|---|---|---|---|
| Age (Years) | 51.5±9.19 | 50.3±10.59 | 0.93 |
| Male | 51 (51%) | 53 (53%) | 0.91 |
| Female | 49 (49%) | 47 (47%) | 0.76 |
| Hematocrit (Hct.) (%) | 39.3±7.59 | 41.8±3.87 | 0017 |
| Hemoglobin (g/dl) | 10.7 ±2.52 | 12.3±3.15 | 0.0001 |
| Erythrocyte ($x10^9$/µL) | 3.70±1.71 | 4.51±0.95 | 0.0001 |
| Leukocyte ($x10^3$/µL) | 511.6±3.6 | 435.13±7.23 | 0.0001 |
| Platelet counts ($x10^6$/µL) | 301.6±56.7 | 457.15±19.3 | 0.0001 |

**Table-II: Frequency of Low Platelet Counts in Study Subjects**

| Variables | Cases | Controls | P-Value |
|---|---|---|---|
| Normal Platelet Counts | 87 | 97 | |
| Low Platelet Counts | 13 | 03 | 0.0001 |
| Total Subjects | 100 | 100 | |




**Graph I. Frequency of Normal and Low Platelet counts**

## DISCUSSION:

A rigorous search of published medical literature of Pakistan, it is claimed that the present is first study being reported for Platelet counts in long term Proton pump inhibitors (PPIs) users of GERD. In developing countries like Pakistan, the injudicious over use of PPIs is very high[10,11]. It is reported the drug induced thrombocytopenia is a diagnosis of exclusion, and reported incidence is <1% in general population[12]. The present study reports low normal platelet counts in those using the PPIs for long durations; in cases and controls were 301.6±56.7x$10^6$ x$10^9$/µL and 457.15 ±19.3 /µL (P<0.05). Thrombocytopenia was observed in 13% cases versus 3% of controls (P<0.05). The findings are supported by previous studies and cases reports[6,7,13-16]. Mukherjee et al[13] reported case report of Esomeprazole and dex-lansoprazole induced thrombocytopenia recently. They reported dropping of platelet counts as low as 10×103/$mm^3$. They concluded that the low platelet effect is drug class effect equally for all generics. It was added that the low platelet counts are caused by both intravenous and oral routes. Watson et al[17] was the first of reporting a case reported of Pantoprazole induced thrombocytopenia. Subsequently, others[13-15] reported similar effects of PPIs induced thrombocytopenia. The findings are in keeping with the present study. A previous retrospective study by Binnetoglu et al[18] demonstrated Pantoprazole induced thrombocytopenia was found significantly in a sample of 35 patients. However, another retrospective study[8] analyzed 468 hospitalized patients for adverse

effects of PPIs on blood platelet counts. They reported thrombocytopenia was not found after Pantoprazole use[4]. Hayashibara et al[19] and Rudelli et al[20] demonstrated low platelet counts induced by omeprazole therapy. Finally, Ranzino et al[21] reported a case of thrombocytopenia after Esomeprazole and hydantoin use. However, the direct causal relationship of PPI was not established due to concomitant hydantoin use[21]. Evidence based findings of present study in light of above reviewed literature; it appears the PPIs may cause thrombocytopenia. However, we could not elucidate the mechanism of thrombocytopenia induction. This needs further large scientific studies be conducted in animal models for elucidating the mechanism of PPIs induced thrombocytopenia. The present study suggests the causal relationship of PPIs induced thrombocytopenia may be true. The only imperfection of present study is a small sample size hence the findings can`t be generalized. However, the strength of study is claimed by its prospective study design, selection of cases by inclusion and exclusion criteria and long term users of PPIs. It is worth to report the causal relationship of PPIs and platelet counts in long term users, however further large scale studies are recommended.

## CONCLUSION :

The low platelet counts (thrombocytopenia) may occur in those using Proton pump inhibitor for long duration of more than three years. Further large scale studies are recommended to finding the causality of long term PPIs use and thrombocytopenia as these are widely used drugs in Pakistan.

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