

Research Article

Effect of long term use of PPI on high sensitive C-reactive protein, pilot study

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ABSTRACT

Background: proton pump inhibitors (PPIs) one of commonly used medications due to their availability as OTC medications however there are many concerns about the safety of their long-term use. This pilot study aimed to measure the level of high sensitive C-reactive protein level as a risk factor marker for cardiovascular disease in patient use PPIs for long time.

Method: Twenty-four adult patients were incorporated in the study. All patients were taking PPI for at least one year. Those patients considered group A. In addition apparently healthy control group considered as group B. Patient information and blood sample were taken from all participants and the level of hs-CRP were measured.

Results: the age of patients were forty years old, most of them were females. The level of hs-CRP were classified into high, moderate and low. Patients who use ppi for long time have higher level of hs-CRP, however there is non-significant differences hs-CRP were found between group A and group B.

Conclusion: The long-term use of PPIs may cause an increase in the level of hs-CRP level. The long term use of PPIs may not be without health concerns especially on cardiovascular system. Further large-scale study required to investigate these effects.

Keywords: proton pump inhibitors, Long-term use, High sensitive-CRP

INTRODUCTION

Proton pump inhibitors (PPI) first discovered in 1989 with the first member of this group was omeprazole. Since that time, they worldwide used for gastric acid inhibition [1]. These drugs prescribed for many indications such as Gastroesophageal Reflux Disease (GERD), gastric and duodenal ulcers, and in combination with antibiotic for *Helicobacter pylori* eradication. PPIs considered as safe drugs when used as for short-term (4-12 weeks) [2].

Good safety and tolerance of PPIs make them widely indicated. This lead to an exponential increase in PPI use. Their use not usually monitored by a health care providers because many of PPIs are available as over-the-counter medications. In addition, many patients used to use PPIs for long-term result in widespread inappropriate use [3]. The inhibition of gastric acid secretion using long coarse of PPIs may be required as maintenance therapy for treatment of GERD and prevention of gastric and duodenal ulcers during NSAIDs or aspirin administration, thus, long-term maintenance therapy (months or years) of PPI is indicated [4].

The safety of long-term therapy were challenge. Some studies show its well-tolerated and low risk

[5]. However, the long-term therapy with PPIs not approved by the FDA and may have significant adverse effects. Many studies suggested that long-term use of PPIs associated with high risk of premalignant gastric conditions like atrophy metaplasia, gastric polyps and gastric cancer and these risks increased with increase the duration of use [6-8]. In addition long term PPIs use may predispose to vascular dysfunction and an increased risk of cardiovascular disease, dementia, fractures, pneumonia, *Clostridium difficile* diarrhea, hypomagnesaemia, vitamin B12 deficiency, chronic kidney disease and renal failure [9].

There are many clinical studies show the association between the longer duration of PPI exposure (≥ 6 months) and high risk cardiovascular disease. The mechanisms of PPIs cardiovascular effects may not directly related to gastric acid suppression, and the evidence is that H₂-receptor blockers are not cause cardiovascular risk [10, 11]. Retrospective analyses of randomized trials of clopidogrel administration for patients with acute coronary syndromes revealed less benefit of the antiplatelet

agent when esomeprazole was co-administered. However, the adverse effect of PPIs is not entirely due to a metabolic drug-drug interaction with clopidogrel because other PPIs (like pantoprazole and rabeprazole) that do not interact metabolically with clopidogrel also attenuate the benefit of this antiplatelet therapy. Additionally, usage maybe associated with myocardial infarction regardless the use of drugs (such as clopidogrel) [12].

C-reactive protein is an acute phase reactant synthesized primarily in the liver and increases in the blood with infection or inflammation as well as following a heart attack, trauma. or surgery. Therefore, this test usually performed when acute or chronic inflammation are suspects such as rheumatoid arthritis, systemic lupus erythromatosus (SLE) or acute infection. To detect lower levels of CRP (0.3 to 1.0 mg/dL), high-sensitivity CRP recommended, as the usual CRP detection tests become less precise [13]. Hs-CRP generally reported in mg/L. Lab values and used for cardiac risk stratification levels of hs-CRP less than (1 mg/dL) reflect a low risk, levels of (1- 3 mg/dL) considered as moderate cardiovascular risk and a level more than (3 mg/dL) is high risk of cardiovascular disease [14, 15].

MATERIALS AND METHOD:

Study design

The data collected from December 2019 to February 2020 from interviews and discussion with the patients and information form files of patients, prescription, or medications they carry with them and then blood samples from patient vein withdrew by small needle, then taken to the laboratory, and analyzed.

Inclusion criteria

Forty-eight adult patients with the mean age of 51.5 years recruited for this pilot study and classified into two groups. Group A (24 patients)

includes patients taking PPI for at least one year, while group B (control group) includes apparently healthy patients. Ethical approval was taken from ethical committee in collage of pharmacy/university of Basra. In addition a detailed information about the study given to all persons who included in the study.

Exclusion criteria:

Exclusion was patients that already has cardiovascular events like myocardial infarction (MI), heart failure or arrhythmia), and patient with certain types of inflammatory bowel disease, such as ulcerative colitis and Crohn's disease. In addition to patients with cancer, severe organ tissue injury, patients with acute infections like high fever, diarrhea, and unconscious patients.

Analytical studies

A lavender type tube used for the collection of 5ml blood sample in each tube and centrifuged to separate the plasma that should be stored in a refrigerator. Each blood sample centrifuged and the General CRP test carried out at the hospital's serology lab .Then the laboratory analyses carried out later in a Clinical Laboratory for high Sensitivity CRP test.

Statistical study:

Statistical analysis performed using Microsoft Excel program. Analytical t-test used to perform comparison between the two groups. The calculated p values of bellow 0.05 considered as significantly different.

RESULTS:

Demographic in table (1) show that the patients age were above fifty years old, most of them were females. The disease and drug of the included patients were mention bellow. Most of the included patients (22 (91.66%) who use PPIs for long term (more than one year) have negative results of direct CRP.

Table 1: Demographic data of all participants.

Parameter		No. (%)
Age	Mean (year)	51.5
sex	female	16 (66.6%)
	male	8 (33.3%)
medications	Statins	3 (12.5%)
	Aspirin	7(29%)
	NSAIDS	4(16.6%)
	Corticosteroid	1(4.16%)
	Gabapentin	2(8.3%)

	Anti-hypertensive	9 (37.5%)
	Anti-diabetic drugs	5 (20.8%)
	Antispasmodic (librax)	2 (8.3%)
Diseases	Hypertension	12 (50%)
	Hyperlipidemia	11 (45.8%)
	Diabetes	5 (20.8%)
	Arthritis	7 (29.16%)
	Asthma	1 (4.16%)
	kidney diseases	3 (12.5%)
	H-pylori	1 (4.16%)
	Thyroid disease	1 (4.16%)
	Irritable bowel syndrome (IBS)	1 (4.16%)
	Anemia	2 (8.3%)
	UTI infection	2 (8.3%)
	Osteoporosis	1 (4.16%)
	Prostatitis	1 (4.16%)
	Cholestasis	1 (4.16%)
Direct CRP	Positive	2 (8.3%)
	Negative	22 (91.66%)

In table 2 shows the classification of each group according to the cardiovascular risk into high (more than 3mg/dl), moderate (1-3mg/dl) and low (less than 1mg/dl). PPIs users show high level of Hs-CRP in high risk group. However non-significant difference have been seen when compare PPIs group with control group.

The figure 1 shows that 50% of PPI users have high level of hs-CRP while 25% of the included patients have moderate and low level.

Table 3 illustrate that there is non significant difference in average level of hs-CRP between PPIs users group compare with control.

Table 2: Classifications of patients according to their cardiovascular risk depending on level of Hs-CRP

Risk	PPI users	Control	P value
High	8.42±5.51	4.04±0.36	0.2045
Moderate	2.36±0.44	2.49±0.47	0.69
Low	0.75±0.097	0.81±0.005	0.3030
p-value	0.001	0.334	-----

*Statistically significant compared to control group (p<0.05).

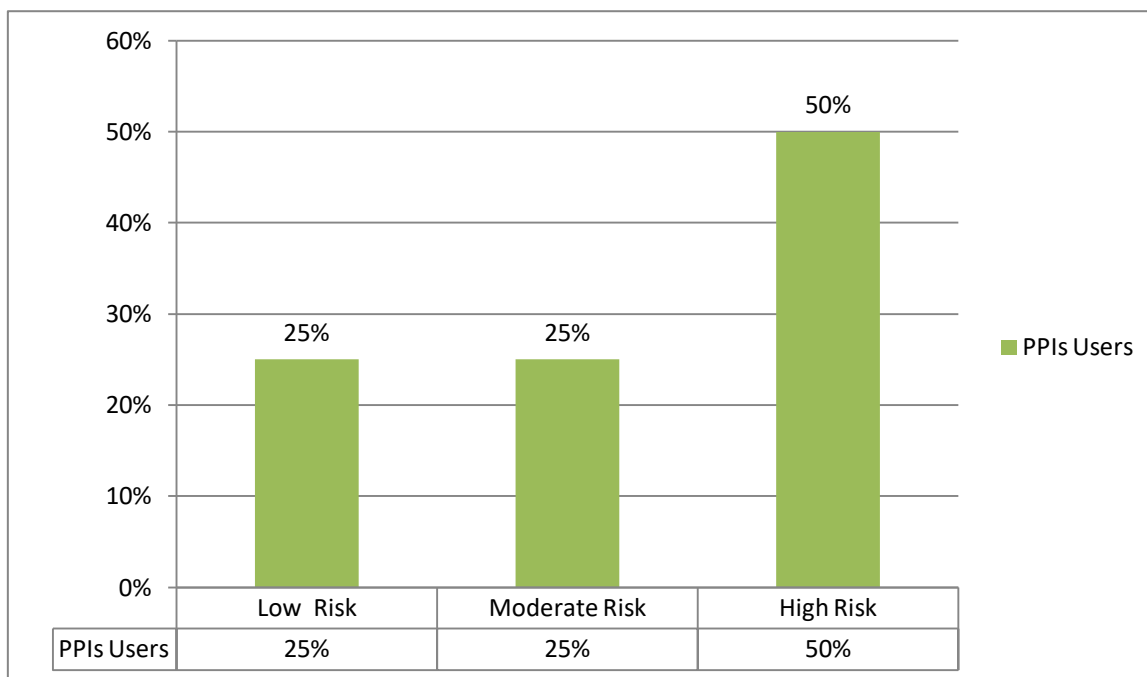


Fig.3: Classifications of patients using PPIs according to their cardiovascular risk depending on level of Hs-CRP

Table 3: Level of hs-CRP in PPI users and control (no PPI).

HS-CRP (Mean \pm SD)		
PPI users	Control	P value*
4.9 \pm 5.10	2.92 \pm 1.16	1.02

P values of <0.05 is statistically significant compared to control group.

DISCUSSION

Proton pump inhibitors are widely used in Iraq due to wide range of indications and good safety profile as well as availability as OTC medication. However, its indication as POM or OTC for GIT conditions like GERD, peptic ulcer recommended for short time in most conditions. It's usually used for four to eight weeks of treatment to provide a symptoms relief followed by either on-demand or maintenance PPI therapy according to the condition and its clinical severity (16). Clinical guidelines recommends minimizing a dose, using "on-demand" or stopping dosing of PPI in patients who have completed a course of 4 weeks of PPI treatment for mild to moderate gastroesophageal reflux disease (GERD) or esophagitis, and their symptoms have been resolved (17).

There is some recent evidence indicating that improper use of PPI is rising. Patients take them without restrictions directly from the pharmacy. Overuse of PPI's lead to their abuse therefore there is evidence of long term adverse effects as well as increase pharmaceutical health-care expenditure (18).

The present pilot study aim to determine if the PPI use is associated with an increase in cardiovascular risk when used for longer duration. All the patients who included in the study use omeprazole for at least one year. Omeprazole is available in multiple forms under many generic products in Iraq, It is cheap, OTC and dispensed without restriction in community pharmacies. The majority of patients in the study were above the age of 40 years (mean age: 51.5 years), Most of them were females [n=16 (66.6%)]. The prevalence of GIT diseases increases with age, which may be explained by age related functional changes to the organs such as lower esophageal sphincter and decreased bicarbonate secretion, also, older people can be more susceptible to the effects of drug interactions due to the use of multiple medications.

Additionally, some of the patients included in our study were complaining from arthritis [n=7 (29.16%)] and they were taking NSAIDs [n=4 (16.6%)] and/or Aspirin [n=7 (29%)]. Upper gastrointestinal bleeding and ulcer are relatively common during aspirin and NSAIDs administration and, therefore, many patients are treated with maintenance doses of proton pump

inhibitors given for longer duration to reduce their complain (19).

Some studies hypothesized that PPIs, if taken at the same time with aspirin, it will alter the pharmacokinetics of aspirin, and this might account for a decline in bioavailability (20, 21). Therefore, PPIs decrease the risk of gastrointestinal bleeding but it might increase the risk of major cardiovascular events but the direct clinical data that evaluate the risk of this interaction are limited, hence it is not confirmed and stills as conflict of interest.

Many studies suggest that the cardiovascular adverse effect of ppl is related to interaction with clopidogrel so PPIs may attenuate the cardiovascular protection of clopidogrel (22). This interaction caused by the enzyme inhibition effect of PPIs to the cytochrome (CYP) P450 isozyme 2C19, which responsible for conversion of clopidogrel to its biological active metabolite. Omeprazole is a more potent inhibitor than any other PPI do (23,24). Therefore the patients who take clopidogril are excluded in this study.

However many studies (including our study) suggest that the cardiovascular risk is still exist in patients who use PPI regardless clopidogrel use (25). Those studies based on evidence that H2-receptor blockers cause reduction in gastric acidity without increase in cardiac risk (25). In addition cardiovascular risk still exist even when antiplatelet drugs other than clopidogrel, like ticagrelor which not required hepatic activation are co-administered (26).

Therefore PPIs may have an independent effects on the cardiovascular system that not related to the alteration in drug absorption(by gastric pH change) and PPI drug–drug interaction (due to enzyme cytochrome p450 inhibition). There are several possible mechanisms by which the long-term use of PPIs could increase the risk of cardiovascular disease. One of the suggested mechanism is that PPIs increase the level of asymmetric dimethylarginine (ADMA) in the plasma which leads to reduced nitric oxide (NO) production by endothelial cell (27, 28, 29, 30). Regardless the possible mechanism by which cardiovascular risk is occur, these risks could assessed by various mechanisms including measuring of hs-CRP.

High sensitive-CRP is a marker that recently added to a cardiovascular risk prediction. However, hs-CRP retains an independent association with incident cardiovascular events after adjusting for total cholesterol, HDL cholesterol, and family history of coronary disease (31, 32).

The present pilot study aimed to discover whether the patients who use PPI for a year or more,

without use of clopidogrel, and evaluate their cardiovascular risk by measuring the hs-CRP level. The relative risk of future cardiovascular events based on hs-CRP testing estimated as follows: low risk: CRP < 1.0 mg/L, intermediate risk: CRP 1.0-3.0 mg/L and high risk: CRP > 3.0 mg/L. (33)

The study shows that a higher percentage of group A have a high level of hs-CRP {n=12(50%)} compared with moderate {n=6(25%)} and low risk group {n=6(25%)} , this result shows that patients who use omeprazole for more than one year may have a higher risk for cardiovascular disease.

This study reveals that hs-CRP values are higher in-group A even non significantly [as shown in table 3] ,who take omeprazole for ≥ 1 year, than the control group B ,who do not use omeprazole. This probably due to low number of patients included in the study and short duration of study.

However, a larger group of patients is needed, in addition, more specific biomarkers like nitric oxide and asymmetric dimethyl arginine (ADMA) as well as other parameters like lipid profile and blood glucose, should be measured to ensure these results and exclude the interfering parameters.

At the end, the physicians and community pharmacists should pay more attention regarding the dispensing of PPI, and they should advice their patients about the proper duration of PPI intake to ensure the safe and effective use of them.

CONCLUSION:

Despite the safety and availability of PPI, more attention should be paid to prevent the unnecessary use for long duration. The unnecessary use of omeprazole more than one year may not be without consequences, it is may cause elevation of hs-CRP level of and hence possibly associated with higher risk of cardiovascular disease. Therefore physicians and pharmacists should be aware about long-term PPI treatment and if used should periodically review patients symptom resolution and treatment tolerability.

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Conflict of interest

The author declare that there is no conflict of interest.

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none

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