

ORIGINAL ARTICLE

COMPARISON OF THE EFFICACIES OF PROTON PUMP INHIBITORS AND H₂ RECEPTOR ANTAGONISTS IN ON-DEMAND TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE

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Abstract

Objective: On-demand treatment protocols in the maintenance treatment of gastroesophageal reflux disease (GERD) are cost-efficient and easy-to-use treatments. This study aimed to compare the efficacies of H₂ receptor antagonists (H₂RA) and proton pump inhibitors (PPI) in on-demand treatment of GERD.

Methods: Patients with persistent GERD symptoms were enrolled between January–November 2015 and were randomly separated into two equal groups. The patients in the first group were commenced on ranitidine 300 mg as H₂RA and the patients in the second group were commenced on pantoprazole 40 mg. A 4-point Likert-type scale generated by the researchers was applied to evaluate the frequencies of reflux symptoms and their impacts on activities of life and business life.

Results: Fifty-two patients were included, of whom 26 (50.0%) were in the PPI group and 26 (50.0%) were in the H₂RA group. There were no significant differences between the study groups both before and after treatment in terms of the severity of reflux symptoms. There were significant decreases in the H₂RA group in terms of the domains of retrosternal burning sensation, regurgitation, nausea and vomiting, and burping ($p=0.036$, $p=0.027$, $p=0.020$, and $p=0.038$, respectively).

Conclusion: PPIs and H₂RAs were both effective in maintaining symptom control and improving the limitations in work or activities in on-demand treatment. Nonetheless, the higher amount of the medication use in the H₂RA group compared with the PPI group led us to conclude that using PPIs during on-demand treatment might be more appropriate than using H₂RA in this setting.

Key Words: Gastroesophageal Reflux, Proton Pump Inhibitors, Histamine H₂ Antagonist

Introduction

Retrograde passage of gastric content into the esophagus is a physiological condition and this is called gastroesophageal reflux disease (GERD) when the imbalance between protective and catalyzing mechanisms causes symptoms or complications (1–3). Goals of treatment of GERD include keeping retrosternal burning sensation and regurgitation symptoms under control, recovering esophagitis, preventing complications, and maintaining remission (1,4). While 80% of patients need acid-suppressing treatments, relapse is observed in 70–80% of patients after treatment (4). In maintenance treatment, continuous medication use leads to high costs and a decrease in the treatment adherence (3–5). Thus, intermittent and on-demand treatment protocols are cost-efficient and easy-to-use treatments (4). Indeed, in a study, it has been shown that patients commonly prefer intermittent or on-demand treatment (6). In the literature, while there are studies showing that both continuous use and on-demand use of proton pump inhibitors (PPIs) in GERD treatment have similar efficacy, there are also studies showing contrary results (4,7–9). On the other hand, studies have reported that PPIs are more effective than H₂ receptor antagonists (H₂RAs) but have higher costs (10,11).

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Excessive bacterial growth in the stomach due to hypochlorhydria, vitamin B12 deficiency, iron deficiency, osteoporosis, and *Clostridium difficile* infection are observed owing to the long-term use of PPIs and tolerance development is observed as a result of the long-term use of H2RA (2–4,12). In the present study, we aimed to compare the efficacies of H2RAs and PPIs in on-demand treatment in patients with GERD.

Methods

Study Population

Patients between 18 and 75-years-old who admitted to the Gastroenterology Clinic of Kartal Dr Lutfi Kirdar Training and Research Hospital with the diagnosis of persistent GERD between January 2015 and November 2015 were included. All patients were on treatment for persistent GERD and eligible for maintenance therapy.

Study Protocol

A 4-point Likert-type scale generated by the researchers was applied to all the patients to evaluate the frequencies of reflux symptoms and their impacts on quality of life (QoL) and business life. The patients were randomly divided into two equal groups. As an on-demand treatment, the patients in the first group were commenced on ranitidine 300 mg as H2RA, and the patients in the second group were commenced on pantoprazole 40 mg. Following the four-week treatment, same questionnaire was applied to all patients again. The patients were also questioned about how many tablets they received in a week at their weekly visits. The study was approved by the local Ethics Committee of Kartal Dr. Lutfi Kirdar Training and Research Hospital (Protocol No: 89513307/1009/508) and the informed consents were obtained from all patients.

The Scales Used in the Study

Severity of reflux symptoms were evaluated using the 4-point Likert scale covering domains of retrosternal burning sensation, regurgitation, nausea and vomiting, and burping. In the same questionnaire, impacts of GERD on QoLor business life within the last four weeks were evaluated through the following questions prepared by Short Form (SF)-36 QoL questionnaire: "Cut down the amount of time you spent on work or other activities", "Accomplished less than you would like", "Were limited in the kind of work or other activities", "Had difficulty performing the work or other activities", and "How much bodily pain have you had during the past four weeks". Validity and reliability study for the Turkish version of SF-36 QoL questionnaire was carried out by Kocyigit et al (13).

Exclusion Criteria

Patients who had esophagitis or extraesophageal symptoms, those with chronic renal impairment and chronic hepatic impairment, and patients who were pregnant patients at admission were excluded. Additionally, patients receiving any acid inhibitor treatment within the last four weeks were excluded in order to exclude the patients on a maintenance therapy.

Statistical Analysis

Data were analyzed using the IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Numerical variables were expressed as mean, standard deviation, median and range (minimum-maximum) and categorical variables were expressed as numbers and percentages. The Mann-Whitney U test was used for intergroup comparisons of abnormally distributed variables and the Wilcoxon signed-rank test was used for intragroup comparisons of non-normally distributed variables. In addition, Student-t test was used to analyze continuous variables, if the distribution was normal. Fisher's exact test was used for the analysis of categorical variables. A p value <0.05 was considered statistically significant.

Results

In the study, 52 patients were included, of whom 26 (50.0%) were in the PPI group and 26 (50.0%) were in the H2RA group. While 21 (80.8%) of the patients receiving PPIs were female and their mean age was 38.5±14.0 years; 18 (69.2%) of the patients receiving H2RA were female and their mean age was 42.4±12.4 years (p=0.52 and p=0.25, respectively). There were no significant differences between the study groups both before and after treatment in terms of the severity of reflux symptoms and having problems in work or activities (p>0.05 for each). According to the intragroup comparisons of the PPI and H2RA groups, there were significant decreases in the H2RA group in terms of the domains of retrosternal burning sensation, regurgitation, nausea and vomiting, and burping (p=0.036, p=0.027, p=0.020, and p=0.038, respectively). The severity of symptoms before and after medication in the PPI and H2RA groups were summarized on Table 1. According to the SF-36 QoL questionnaire, a significant decrease was observed only in the domain of "accomplished less than you would like" in the H2RA group (p=0.04). Additionally, there were significant decreases in the domain of bodily pain in the PPI and H2RA groups (p=0.034 and p=0.006, respectively). Severity of having problems at work or during activities before and after medication in both groups were summarized on Table 2.

The mean of the amount of medication received was 5.04±2.07 in the PPI group and 10.46±4.09 in the H2RA group in the first week (p<0.001). Besides, the median of the amount of medication received was 5.0 (0.00-7.00) in the PPI group and 9.5 (0.00-14.00) in the H2RA group in the fourth week (p=0.002). The amount of medication received by the patients was evaluated weekly and no significant change was identified in both groups from first to fourth week (p=0.32 for PPI group and p=0.09 for H2RA group).

H2RA with a short-term rapid efficacy is another medication used as on-demand treatment; however, its most important disadvantage is to cause tolerance development after 2-week continuous use (19). On the other hand, it has been reported that on-demand treatment with H2RAs would result in less tolerance development (20). In the studies, it has been reported that on-demand treatment with H2RAs provides a regression in retrosternal burning sensation (21,22). Correlatively with the literature, in the present study, on-demand treatment with H2RA led to a decrease

Table 1. Severity of symptoms before and after medication in the study groups

	PPI Group (n=26)			H2RA Group (n=26)		
	Before	After	p	Before	After	p
Retrosternal burning sensation	1.5 (0.0-3.0)	1.0 (0.0-3.0)	0.286	2.0 (0.0-3.0)	1.0 (0.0-3.0)	0.036
Regurgitation	2.0 (0.0-3.0)	1.0 (0.0-3.0)	0.062	2.0 (0.0-3.0)	1.0 (0.0-3.0)	0.027
Nausea and vomiting	1.0 (0.0-3.0)	0.5 (0.0-3.0)	0.131	1.0 (0.0-3.0)	0.5 (0.0-3.0)	0.020
Burning	1.5 (0.0-3.0)	1.0 (0.0-3.0)	0.142	2.0 (0.0-3.0)	1.0 (0.0-3.0)	0.038

H2RA:H₂ Receptor Antagonist; PPI: Proton Pump Inhibitor
 Data are presented as median (minimum-maximum).
 Wilcoxon Test

Discussion

Treatment of GERD is focused on reducing symptoms stably, recovering major esophageal lesions, and preventing complications (4). Approximately 75% of patients report relapsing symptoms after pretreatment is discontinued and this increases costs substantially (1,14,15). Therefore, it is aimed to conduct maintenance therapy with a minimum number of medications in a cost-effective way in a long-term management of the disease (14,15). As a result, on-demand treatment is an acceptable and a cost-effective protocol for relieving the symptoms of GERD (1). In the present study, we aimed to evaluate the efficacies of PPIs and H2RAs in the on-demand treatment of patients with GERD. In a previous study, on-demand treatment of GERD with omeprazole was found to be effective in most of the patients (16). In other studies, esomeprazole was shown to be effective in the management of long-term symptoms of patients with GERD (7,8). In a study performed in patients with low-grade esophagitis, symptom control could be achieved in more than 85% of the patients by the 6-month on-demand treatment with rabeprazole (17). Another study also reported a decrease in symptoms by the on-demand treatment with 10 mg rabeprazole (18).

in the complaints of retrosternal burning sensation, regurgitation, nausea, vomiting, and burping. In a study comparing rabeprazole and ranitidine treatments, no significant difference was found between two groups in terms of symptom relief, amount of medication received, and the number of days without medication (23). In the present study, although there was a decrease in the severity of all complaints of GERD in both study groups, only a statistically significant decrease was observed in the H2RA group. One of the most important reasons for this discrepancy might be attributed to the short monitoring period in the present study. The shorter efficacy period of H2RAs than PPIs might be another reason. There are evidences showing that GERD has a significant impact on QoL and may prevent daily activities and that the treatment may provide significant improvement on QoL (1,24). In the present study, an improvement was observed in the domain of difficulty in performing the work or other activities after treatment in both study groups; however, a significant improvement was found only in the domain of accomplished less than you would like in the H2RA group. Additionally, there was a significant decrease in the domain of bodily pain in both groups. The reason for this discrepancy might be attributed

Table 2. Severity of having problems in work or activities before and after medication in the study groups

	PPI Group (n=26)			H ₂ RA Group (n=26)		
	Before	After	p	Before	After	p
Cut down the amount of time you spent on work or other activities	11.0 (42.3)	5.0 (19.2)	0.654**	11.0 (42.3)	6.0 (23.1)	0.209**
Accomplished less than you would like	14.0 (53.8)	4.0 (15.4)	0.359**	9.0 (34.6)	5.0 (19.2)	0.04**
Limitation in the kind of work or other activities	9.0 (34.6)	3.0 (11.5)	0.268**	14.0 (53.8)	5.0 (19.2)	0.186**
Difficulty in performing the work or other activities	12.0 (46.2)	7.0 (26.9)	0.130**	12.0 (46.2)	6.0 (23.1)	0.209**
Bodily pain	4.0 (2.0-6.0)	3.0 (2.0-6.0)	0.034*	3.5 (2.0-6.0)	3.0 (2.0-6.0)	0.006*

H₂RA:H₂ Receptor Antagonist; PPI: Proton Pump Inhibitor
Data are presented as n (%) or median (minimum-maximum), where appropriate.
*Wilcoxon Test; **Fisher's Exact Test

to the short monitoring period in the present study. One of the limitations of the present study is the short monitoring period, which makes it difficult to do the assessment of drug efficacy differences between groups. Another limitation is the lower number of subjects. Consequently, there is only one study in the literature evaluating the effects of on-demand treatment with PPIs and H₂RAs on reflux symptoms (23). The findings of the present study suggested that in on-demand treatment, either PPIs or H₂RAs was effective in maintaining symptom control and improving the limitations in work or activities in the patients with GERD. However, there was only a statistically significant decrease was observed in the H₂RA group. H₂RA affected on gastric acid production more quickly, but its duration of action was lower. Although these effects appeared to be more significant with the use of H₂RA, the higher amount of the medication use in the H₂RA group compared to the PPI group led us to conclude that using PPIs during on-demand treatment might be more appropriate than using H₂RA in this setting.

Table 3. Amount of medication received by the study groups according to the treatment weeks

	Study Groups		p
	PPI	H ₂ RA	
1st week	5.04±2.07	10.46±4.09	<0.001^d
2nd week	4.81±2.26	9.73±4.33	<0.001^d
3rd week	5.0 (0.0-7.0)	10.0 (0.0-14.0)	0.001^{bb}
4th week	5.0 (0.0-7.0)	9.5 (0.0-14.0)	0.002^{bb}

PPI: Proton Pump Inhibitor; H₂RA:H₂ Receptor Antagonist
Data are presented as mean±standard deviation and median (minimum-maximum)

^dStudent-t Test; ^{bb}Mann Whitney U Test

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