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Original Research

Effectiveness of proton pump inhibitor (Rabeprozole) in nonerosive reflux disease: a prospective placebo-controlled study

Hakim Mohammad Shafi[1], Showkat Hussian Shah[2], Aijaz Ahmad Hakeem[3]

[1]Consultant Medicine, Govt. Medical College Anantnag, Jammu and Kashmir, India;
[2]Consultant Medicine, Govt. Medical College Anantnag, Jammu and Kashmir, India;
[3] Consultant Radiologist, Government Medical College, Srinagar 190010, Jammu and Kashmir, India

***ABSTRACT*:**
Introduction: Nonerosive reflux disease is defined as the presence of typical symptoms of gastroesophageal reflux disease in absence of visible esophageal mucosal injury at endoscopy. 24 hour ph study is needed to define the sub group. Treatment with the acid inhibitory agents is effective, proton pump inhibitors are most effective form of therapy. Clinical results to date suggest that antisecretory therapy may be less effective in providing symptom relief for the patients nonerosive reflux disease than the patients with erosive disease. **Material and Methods**: A total of 101 patients with nonerosive reflux disease were randomized to receive placebo (49) or rabeprozole (52) for 6 months, with consultations at 3 weeks, 6 weeks, and 6 months. The primary end points were change in the severity of heart burn and regurgitation at the above mention period. Demographics of the randomized in each group were comparable. **Results:** The baseline characteristics between two groups were similar.At 3 weeks and six weeks, treatment group showed greater reduction of VAS for heart burn($p<0.01$). However there was no significant difference between the placebo and rabeprozol group at 6 weeks and 6 months. Around 56.43% patients showed demesseter's score more than than 20 and where consider to have positive 24 hour ph study. Patients who had positive 24 hour ph study responded moderately well to Rabeprozole (59.61%) compared to placebo, Patients on placebo showed only mild response in only 20.40% patients and 79.59% patients had no response. **Conclusion:** Rabeprozole was more effective than placebo of the treatment of symptoms presented by the patients with nonerosive reflux disease, who had positive 24 hour ph study. From the observations of the present study it could be concluded that Among GERD, Nonerosive reflux disease more common than erosive esophagitis. Nonerosive reflux disease is a heterogeneous disorder comprising three different groups, Haitus hernia less common endoscopic finding in nonersive reflux disease. From the present study it is concluded that Rabeprazole is effective in controlling the symptoms in NERD patients and effect of the drug is better than the placebo in the patients who had positive ph study which was defined by Demesseter's score more than 20.
Key words: Proton pump inhibitor, non erosive reflux disease.

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Corresponding Author: Dr. Hakim Mohammad Shafi, Consultant Medicine, Govt. Medical College Anantnag, Jammu and Kashmir, India;

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INTRODUCTION

Gastroesophageal reflux disease is very common disorder, affecting up to 20% of the population in North America, 9% to 17% of Europe, 12% to 15% of Australia, and 2% to 5% of Asia once a week.[1]It has been assumed that patients with gastroesophageal reflux disease symptoms who lack esophageal mucosal injury represent a mild form of the disease. About 50% with frequent reflux symptoms in the community seek care; a minority undergoes investigation, with only one in five having an EGD and one in 10 consulting a gastroenterologist.[2]

Currently there are no clinical features that can distinguish patients with nonerosive reflux disease from those with erosive esophagitis or even those with Barrett's esophagus. Severity, frequency, or intensity of symptoms has been shown consistently to be similar among the

different gastroesophageal reflux disease phenotypes.[3]There have been some suggestions in the literature that nonerosive reflux disease patients are more commonly reporting associated dyspeptic symptoms than other gastroesophageal reflux disease phenotypes.[4] However, symptoms such as bloating, early satiety, nausea, and vomiting are commonly reported by all gastroesophageal reflux disease phenotypes and presently do not appear to afflict any specific group more than the other. In contrast, functional heartburn patients report chest pain significantly more common than their counterparts within the nonerosive reflux disease group.[5]Additionally, nonerosive reflux disease may present with cough, wheezing, sore throat, chest pain, and other extraesophageal manifestations. Furthermore, insomnia, dyspeptic symptoms, and other functional bowel symptoms may also be reported by patients with nonerosive reflux disease

Patients with classic symptoms of gastroesophageal reflux disease and normal esophageal mucosa have been classified as having endoscopy-negative reflux disease, symptomatic gastroesophageal reflux disease, or nonerosive reflux disease.[6] A group of experts at the Genva Workshop on Reflux Management offered the following definition of patients with nonerosive reflux disease: "These are individuals who satisfy the definition of gastroesophageal reflux disease but do not have either Barrett's esophagus or definite endoscopic esophageal breaks."[7] A similar definition, proposed by Waring, is "burning retrosternal discomfort for at least three months, but with normal esophageal mucosa on upper endoscopy."[8]

Early studies reported that approximately 50% of patients with heartburn were found to exhibit normal esophageal mucosa during endoscopy.[9] However, several community-based European studies of nonerosive reflux disease found a much higher prevalence of 70%.[10]Galmiche et al. assessed the efficacy of on-demand H_2-receptor antagonist therapy in patients with gastroesophageal reflux disease symptoms who were recruited from general practice clinics. [11]A total of 423 patients were included in the intent-to-treat analysis of this study; 71% met the criteria for nonerosive reflux disease. Among patients with nonerosive reflux disease, between 30% and 50% have normal 24-hour esophageal pH monitoring, defined by duration of acid exposure (pH <4) over a period of 24 hours, and thus meet the diagnostic criteria set for functional heartburn. [10,12] In a recent study, Martinez et al.evaluated 71 nonerosive reflux disease patients and demonstrated that in 50% who underwent pH testing, normal distal esophageal acid exposure was present.[13] Of those with functional heartburn, approximately 40% have the hypersensitive esophagus.

However, it should be consider that most patients with gastroesophageal reflux disease symptoms never seek medical attention. It is still unknown what percentage of these nonpresenters has nonerosive reflux disease or functional heartburn. Additionally, there are very few studies that can shed light on the clinical characteristics of nonerosive reflux disease, particularly compared with erosive esophagitis. Nonerosive reflux disease patients have a slightly higher rate of failed peristaltic contractions, defined as nontransmitted contractions or contraction waves that do not traverse the entire esophagus. Additionally, nonerosive reflux disease patients demonstrate mildly reduced mean lower esophageal sphincter resting pressure and distal amplitude contractions as compared with normal subjects[14]

Hiatal hernia is a relatively uncommon anatomic finding in nonerosive reflux disease patients as compared with patients with erosive esophagitis or Barrett's esophagus. Regurgitation may also affect patients with nonerosive reflux disease and can present as bitter or sour taste in the mouth. Regurgitation is less common than heartburn and more difficult to control with antireflux treatment. As a result most of the patients with nonerosive reflux disease require long-term treatment with antireflux medications. Thus far, we lack any clinical evidence that patients with nonerosive reflux disease are at risk of developing any of the typical complications of gastroesophageal reflux disease, Barrett's esophagus, or adenocarcinoma of the esophagus over time. The main impact of the disease is on patients' perception of their quality of life.

The purposes of medical therapy for GERD are to relieve symptoms, to heal esophageal mucosal damage, and to prevent the development of complications. Maximizing therapy for the patient with symptomatic GERD is based on an understanding of the multiple lifestyle, pharmacologic, endoscopic, and surgical options for treatment. According to the American College of Gastroenterology (ACG) guidelines, acid suppression is the mainstay of therapy for GERD. PPIs provide the most rapid symptomatic relief and heal esophagitis in the highest proportion of patients;[15]therefore, PPIs are the first choice for patients who have moderate or severe GERD or complications. Treatment of GERD is based on the concept that gastric contents, principally acid and pepsin, are responsible for esophageal mucosal injury and symptoms.[16]The basic principle of pharmacologic management of GERD is the control of intragastric pH, which correlates with esophageal healing[17]and subsequently symptom relief has recently been suggested.

Approximately 1 billion parietal cells line the gastric mucosa and secrete acid into the gastric lumen in response to various neurocrine, paracrine, and endocrine factors.[18] One of these factors, histamine, leads to increased hydrogen ion secretion by reversibly binding to histamine-2 (H_2) receptors on parietal cells . H_2-receptor antagonists (H_2RAs), such as cimetidine, nizatidine, ranitidine, and famotidine, reversibly block H_2 receptors and decrease basal and meal-stimulated acid secretion. It is

here that PPIs exert their mechanism of action and suppress gastric acid secretion.PPIs inhibit proton pumps that are actively secreting acid. Following a meal, only 70% to 80% of proton pumps will be activated at any given time. Therefore, only about 70% to 80% of pumps are inhibited with the first dose of a PPI. The pKa of the PPI may theoretically impact its stability and its rate of activation. Pantoprazole, with a pKa of 3.96, is activated slowly at a high pH, whereas Rabeprazole, with a pKa of 5, is activated more rapidly. Theoretically, this may lead to Rabeprazole being activated outside theparietal cell.

The aim of the present study was to access prospectively the effectiveness of proton pump inhibitor (Rabeprazole) versus placebo in nonerosive reflux disease.

MATERIAL AND METHODS

A randomized, prospective study was conducted in department of medical gastroenterology Shere-i-Kashmir Institute of Medical Sciences Soura Srinagar, a tertiary care hospital, to study the effectiveness of proton pump inhibitors in non erosive reflux disease. The research proposal was approval from institutional review board Ethical committee of the institute. Data was prospectively collected from all the patients who presented with the classic symptoms including heartburn and/ or regurgitation, but who did not have either Barretts or definite endoscopic esophageal mucosal breaks (esophageal mucosal erosion or ulceration) were referred to have endoscopy negative reflux disease.

Subjects were enrolled from both sexes, with age between 18 and 65 years. The included patients were asked to discontinue antacids, metaclopromide, cisapride, H2 blocker and proton pump inhibitors for at least 7 days before entering study. Certain Exclusion criteria were set as patients with, age less than 18 years or above 65 years, ischemic heart disease, history of partial or total gastrectomy, strictures, pregnancy and lactation, endoscopic evidence of esophagitis, mental disability, critically or acutely sick patients, active tuberculosis, uncontrolled / badly controlled diabetes, known Hepatitis B patients, HIV positive patients and those who failed to give a positive consent.

The patients were subjected to upper GI endoscopy. Those who fulfilled the above criteria of endoscopy negative reflux disease were subjected to ambulatory 24 hour PH monitoring study. Esophagogastroduodendoscopy (EGD) was conducted in the Endoscopy lab. A patient with the overnight fast was made to lie in semiprone position. Fibropticendoscope (Pentax) was used to look for esophagitis, haitus hernia or peptic ulcer. Enrolled patients with normal Esophagogastroduodenoscopy (EGD) were subjected to 24 hour ambulatory esophageal pH test. Lower esophageal pH was measured with an esophageal probe (in gold Messtechnik AGE Industrie Nord Ch-8902 Urdorf/Switzerland).

Acid exposure was measured as the time the pH in the esophagus was less than 4. 24 hour esophageal acid exposure was measured by using 6 components, 1. % time pH <than 4 for total, supine, upright time, 2.Number of Reflux episodes, 3. Refluxes 5 mts longer, 4. Longest Reflux episode, 5 .Composite score (De. Meester score). Patients who have deMesseter's score of more than twenty (20) were enrolled for the study. [19]

Randomization (procedure for allocating subjects into experimental and control group) All the subjects who fulfilled the criteria of non erosive reflux disease were randomized in order to allocate subjects/patients into study/experimental and placebo group. All the patients with odd enrollment constituted experimental group and all the patients with even enrollment formed our placebo group.

Experimental group received tablet Rabeprozole once a day for three weeks. These patients were given optimal dose (20mg) of this proton pump inhibitor before breakfast. They were on clinical trial of three weeks. Placebo group received identical looking tablet similarly at the same time for the same period of time. After the treatment patients have to answer the one single question on a formula "did you essentially without any doubt, have less heart burn and /or acid regurgitation during the treatment". The question was bipolar with alternative as yes or no. The primary efficacy end-point was the change in severity of heartburn as evaluated by using a visual analog scale at 3weeks, 6weeks and 6th month of treatment compared to baseline in the intention-to-treat population.

RESULTS

Among 101 patients 52 cases were in Rabeprazole group and 49 cases were in placebo followed by raberazole group with 35 males and 17 females in former group and 26 males and 23 females in later group. among 101 cases, in rabeprazol group 22 had Retrosternal burning ,3 regurgitation and 27 with combination of both symptoms. In placebo followed by Rabeprazole group 18 had Retrosternal burning/discomfort , 3 had regurgitation and 28 had both the symptoms. None of the patients had co-morbidity. 34 cases were non smokers and 18 cases were smokers in Rabeprazole group and 40 were nonsmokers and 9 were smokers in Placebo followed by Rabeprazole

In Rabeprozole group, Age ranged from 18 to 65 years with mean age of 37.0 ± 12.6yrs in comparison to 18 to 60 yrs with mean age of 35.2.0 ± 10.5yrs in Placebo group while Weight ranged from 40 to 88 kgs with mean weight of 60.1± 10.5y compared to 45 to 84 kgs with mean weight of 58.1± 7.7kgs in Placebo group.

Table 1 shows the Patients with negative ph study (Demesseters score <20) 81.8% of cases some kind of response to Rabeprozole where as 19.2% showed no response. Patients with positive ph study (Demesseters score ≥20) showed some kind of response 98.2% and 96.5% at 6weeks and 6 month of treatment with Rabeprozole.

Table 2 shows that there was a significant difference in the response rate to treatment at three weeks of treatment between placebo and Rabeprazole group (p-value < .001) However difference was not significant once both groups received Rabeprazole.

Table 3 shows the degree of response in accretion with Demesseter's score in Rabeprazole and placebo group. 31(59.61%) patients had moderately good response which included 13(25%) patients with good response and 18(34.61%) with moderate response.8(15.38%) had no response with the Rabeprazole at three weeks Only 10 (20.40%)patients showed response with placebo while 39(79.59%) showed no response.

Table 1: Response to treatment in accretion with Demesseter's score

Duration		**Demesseter's score <20**	**Demesseter's score >20**	**p-value**
Total cases n (percent)		44	57	
6 weeks	Responders	36(81.8)	56(98.2)	.004
	Non Responders	8(19.2)	01(1.8)	
6 months	Responders	36(81.8)	55(96.5)	0.014
	Non Responders	8(19.2)	2(3.5)	

Table 2: Response to treatment to Rabeprazole verses placebo

Duration		**Rabeprozole**	**Placebo***	**p-value**
Total cases n(percent)		52	49	
3 weeks	**Responders**	44(84.6)	10(20.41)	<0.001
	Non Responders	8(15.4)	39(79.6)	
6 weeks	**Responders**	46(88.6)	47(95.9)	>0.165
	Non Responders	6(11.5)	2(4.1)	
6 months	**Responders**	46(88.4)	47(95.9)	>0.165
	Non Responders	6(11.5)	2(4.1)	

**Patients received placebo up to three weeks shifted to Rabeprazole till end of treatment*

Table 3: Degree of response in accretion with Demesseter's score in Rabeprazole and placebo group

		Rabeprazole		**Placebo follow by Rabeprazole***	
		< 20	**>=20**	**< 20**	**>=20**
Response at 3 Week	**Good response(>70)**	4(20.0)	9(28.1)	0(0.0)	0(0.0)
	Mod(50-70)	3(15.0)	15(46.8)	0(0.0)	0(0.0)
	Mild(30-49)	6(30.0)	7(21.8)	5(20.8)	5(20.0)
	No response<29	7(35.0)	1(3.1)	19(79.1)	20(80.0)
Response at 6 Week	**Good response(>70)**	4(20.0)	13(40.6)	2(8.3)	10(40.0)
	Mod(50-70)	5(25.0)	17(21.8)	9(3.7)	15(60.0)
	Mild(30-49)	5(25.0)	2(6.2)	11(45.8)	0(0.0)
	No response<29	6(30.0)	0(0.0)	2(8.3)	0(0.0)
Response at 6 months	**Good response(>70)**	4(20.0)	15(46.80	3(12.5)	10(40.0)
	Mod(50-70)	6(30.0)	14(43.7)	8(33.3)	15(60.0)
	Mild(30-49)	4(20.0)	3(9.3)	11(45.8)	0(0.0)
	No response<29	6(30.0)	0(0.0)	2(8.3)	0(0.0)

**Patients received placebo up to three weeks shifted to Rabeprazole till end of treatment*

DISCUSSION:

The present prospective study was carried out in Shere-i-Kashmir Institute of Medical Sciences Soura Srinagar, which is a tertiary care hospital in Kashmir. One hundred and fifty-one cases were registered through out-patient department, presenting with the symptoms suggestive of gastroesophageal reflux disease. The study was conducted in the Department of Gastroenterology with the idea that in the literature it was found that heartburn in gastroesophageal reflux disease subjects without esophagitis is less responsive to proton pump inhibitors than heartburn in those with erosive esophagitis.

In the subjects of the study 20.52% had erosions and 79.47% had no mucosal injury and there was no Barrett's esophagus in present study during this period of study. Roshida MS and Goh KL showed that in Asia, nonerosive reflux disease affects up to 65% of the Indians, 72% of the Malay, and 60% to 90% of the Chinese in studies from Malaysia, Singapore, China, and Hong Kong.[20]In the present study Haitus hernia was present only in 08 (07.92%) cases. In a study by Modh SR in an Asian population Hiatus' hernia was found in 6.7% and Barret's esophagus in 2%.The incidence of hiatus hernia resembles the present study possibly due to ethnic origin.[11] Hiatus hernia is fairly a common finding in adults, with estimates of its prevalence ranging from10-80%.

Epidemiological studies have shown that there are differences in clinical characteristics between patients with endoscopy negative reflux disease and erosive esophagitis. In a Japanese study by Yasuhiro Fujiwara, showed that female gender, low BMI, not smoking, absence of hiatus hernia and severity of gastric atrophy were positively associated with endoscopy negative reflux disease compared with erosive esophagitis among GERD patients.[21]In the present study there were both similarities and differences. Most of the patients in the present study were males which were against this study. However most of the in the present study patients were nonsmokers had low BMI, only few had hiatus hernia and lower age with a mean of 36.9% consistent with this study.

In the present study subjects were given drug or placebo as per set protocol and response was recorded at 3week, 6weeks and 6 month interval and patient's response score was recorded as per visual analogue scale, 31(59.61%) patients had moderately good response which included 13(25%) patients with good response and 18(34.61%) with moderate response.8 (15.38%) had no response with the Rabeprazole. Only 10 (20.40%) patients showed response with placebo while 39(79.59%) showed no response.The p-value was significant (<.01) between placebo and drug group. However p value was not significant at 6 weeks and 6 month period possibly as placebo group was shifted to Rabeprazole group after the initial 3 weeks of the treatment.

Non-acid-related stimuli (volume, esophageal motor event, nonacidic reflux, etc.) may trigger classic symptoms of gastroesophageal reflux disease as well. Thus, the axiom "no acid, no heartburn" should be considered obsolete. Heartburn appears to be a cortical perception of a variety of intraesophageal events, of which acid reflux is only one.[22]Therefore reasons for low response could: a)Heterogeneous disorder ,different groups respond differently, b) Functional heartburn has least response to antisecretry drugs, respond to antipsychotic or antidepressant drugs, c) Hypersensitive esophagus has less esophageal exposure to acid and d) Non-acid-related stimuli which includes volume, esophageal motor event, nonacidic reflux, etc.) may trigger reflux symptoms.

57 (56.43%) Patients had positive ph study (Demesseter's score >20) among these 32 patients were put on Rabeprazole and 25 patients were put on placebo therapy among the Rabeprazole group 75% patients had moderately good response, 21.88% did showed only mild response and 3.1% showed no response. The results of the present study are comparable to a 4-wk study by Bate CM, et al on patients with heartburn and normal endoscopy in which omeprazole resulted in complete symptom relief in nearly 60% of patients versus approximately 20% of those receiving placebo.[23]In a similar placebo-controlled trial by Lind T, et al symptom relief was observed at 4 wk in approximately 60% of patients receiving omeprazole versus 24% of those in the placebo group.[10] There are trials comparing the therapeutic efficacy of PPIs versus H_2 RAs and cisapride in patients with NERD. In one study done by Venables TL et al, 60% of patients treated with omeprazole had relief of heartburn, versus 40% of those receiving H_2 RAs.[24]Similarly, in a study by Richter JE, et al in the US, lansoprazole has also been shown to be more effective than ranitidine in relieving symptoms of reflux in patients without esophagitis.[25]Another study by Miner BP Jr et al who's results were comparable with results of the present study which demonstrates that Rabeprazole, 10 mg or 20 mg, provides rapid relief of symptoms in patients with nonerosive GERD.[24]

When combined with previously reported data on the efficacy of Rabeprazole in erosive GERD, these findings suggest that the drug may hold an important therapeutic advantage for patients whose heartburn is treated empirically (i.e., without prior endoscopy).[24]In the present study results showed superiority of Rabeprazole over placebo with a high therapeutic gain 64.21%. Carlssonet al. used 10 mg or 20 mg of omeprazole to treat both endoscopy-negative and endoscopy-positive patients with GERD symptoms.[1] After 4 wk of treatment, symptoms of abdominal pain, epigastric pain, and dysphagia were resolved more often in endoscopy-positive patients than in those without endoscopic findings. Three further randomized, double-blind, multicenter studies involving a total of more than 2 600 patients with NERD treated for 4 week with omeprazole 20 mg, and

esomeprazole 20 or 40 mg revealed comparable success rates (resolution of symptoms in 60-70% of the patients). [26]

From the results of the present study and the reports of the previous studies it may be concluded that appropriately dosed PPI treatment can achieve a satisfactory initial response in some two-thirds of the patients. If initial treatment with 4 week of PPI fails to elicit adequate symptom control , increasing the PPI dose (e.g. standard dose PPI twice daily) is recommended, since studies have shown that patients with acid-sensitive esophagus respond better to a high PPI dose.[27,28]The results of the present study show that patients who had increased esophageal acid exposure showed better response to Rabeprazole than placebo. Martinez SD et al., (2003) found that patients with nonerosive reflux disease demonstrate the lowest esophageal acid exposure profile as compared with patients with erosive esophagitis or those with Barrett's esophagus.[13] Only 45% of the non erosive reflux disease patients demonstrate abnormal values during pH testing as compared with 75% of the patients with erosive esophagitis and 92% of those with Barrett's esophagus. The present study showed that figures slightly more than their study 56.43% vs 45%.

The results of the present study it is concluded that Rabeprazole is effective in controlling the symptoms in NERD patients and effect of the drug is better than the placebo in the patients who had positive ph study which was defined by Demesseter's score more than 20.

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