Original Research

Comparative assessment of response of pantoprazole and combination of pantoprazole withbaclofen in patients of gastroesophageal reflux diseaseby nuclear GR study

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ABSTRACT:
Aim: comparative assessment of response of pantoprazole and combination of pantoprazole with baclofen in patients of gastroesophageal reflux disease by nuclear gr study. **Methods:** A hospital based Prospective study was done in the department of Department of Medicine at Guru Gobind Singh Medical College and Hospital, Faridkot after ethical permission. Total 60 patients of gastroesophageal reflux disease were selected on the basis of findings of upper GI endoscopyfollowed which gastroesophageal reflux scintigraphy was carried out on these patients and then cases with grade 3 gastroesophageal reflux disease were selected. Thereafter, these grade 3 gastroesophageal reflux disease patients were divided into 2 groups having 30 patients each. Group 1:- Patients of gastroesophageal reflux disease grade 3 were treated with pantoprazole(40mg) once daily. Group 2:- Patients of gastroesophageal reflux disease grade 3 were treated with combination of pantoprazole(40mg) once daily with baclofen(10mg) thrice daily. **Results:** Out of total 60 patients who presented with GERD, 27 (45%) weremale and 33 (55%) were female. 32 patients(53.3%) had BMI between 18.5-24.9, followed by 26 patients (43.3%) in 25-29.9 group and 2(3.3%) patients were in <18.5 group. Frequency of occurrence of heart burn, regurgitation, chest pain and hoarseness in patients of GERD before treatment was 49(81.7%), 47(78.3%), 21(35%) and 8 (13.3%) respectively. There was difference in frequency of symptoms after the treatment. Frequency of Heart burn was10(16.7%), Regurgitation was 12(20%), Chest pain was 4(6.7%) and Hoarseness was 2(3.3%). we observe that there was significant improvement notedin Regurgitation after treatment in group 1 -19(66.33%) and group 2- 29(96.7%), with significant p value (p = 0.001). In group 1- 33.3% cases and in group 2- 36.7%cases had chest pain (before treatment). There was non-significant (p=0.301) difference noted in complain of Chest Pain after treatment, in group 1-[3(10%) cases] and group 2 – [1(3.3%) cases]. The above table shows in group 1- 13.3% cases and group 2-13.3%cases presented with hoarseness of voice (before treatment). There was non- significant (p=0.150) difference noted in complain of Hoarseness of voice after treatment, between in group 1 and group 2. The patients of GERD, heart burn improved in 66.7% patients in group 1 and 95.5% patients in group 2 with significant p value (p=0.013), regurgitation improved in 57.7% in group 1 and 95.2% patients in group 2 with significant p value (p= 0.003), chest pain improved in 70% in group 1 and 90% in group 2 with non-significant p value (p = 0.223) and hoarseness of voice improved in 50% in group 1 and 100% in group 2 with non-significant p value (p = 0.102).
Keywords: pantoprazole, pantoprazole withbaclofen, gastroesophageal reflux

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common and chronic gastrointestinal disorder with a significant negative impact on quality of life. Although mortality associated with this is rare. Such patients have reported a lower quality of life than healthy individuals. The actual prevalence of GERD was difficult to obtain because those who seek health care probably, represented only a tip of ice berg.[1,2] A study showed that weekly prevalence of GERD is 7.6% in India.[3] While another study showed its prevalence between 16.2 to 18.7% in India, one more

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study showed prevalence of GERD is 22.2 % in South India.[4] Stomach is a dilated part of alimentary canal between oesophagus and small intestine. It is a muscular sac and J shaped structure. It is divided into four parts; cardia, fundus, body and pyloric.It is located at level of T10 and L3 vertebrae. It secretes four major secretory products - mucus (from mucous cell), hydrochloric acid (from parietal cell), protease (from mucous and chief cell) and hormone gastrin (from epithelium cell). All of these helps in digestive process or control of gastric function. The passage of gastric contents into the oesophagus is a normal physiologic phenomenon.[5] GERD is an incessant digestive disease. It is defined as a condition that develops when the reflux of stomach contents into the oesophagus causes troublesome symptoms or complications.[6] Among the mechanisms thought to contribute to the development of GERD are transient lower esophageal sphincter relaxations (TLESRs) or decreased lower esophageal sphincter (LES) resting tone, impaired oesophageal acid clearance, delayed gastric emptying, decreased salivation, and impaired tissue resistance. A significant defect in any one of these forces can alter the balance from a compensated state to a decompensated one and produces the symptoms and complication of GERD.[7] The completion of esophageal acid clearance with restoration of esophageal pH depends on salivation. Normally, saliva can neutralize any residual acid coating the esophagus after a secondary peristaltic wave. Acid clearance is prolonged by a reduced salivary rate or by diminished salivary capacity to neutralize acid. Reduced salivation during, or immediately before, sleep accounts for markedly prolonged acid clearance times.[7] Reduced oesophageal acid clearance during sleep appears to be a major causative factor in serious forms of GERD.[8] Reduced frequency of swallowing-induced peristalsis during sleep also prolongs oesophageal acid exposure.

Treatment modalities for GERD patients are lifestyle modifications (raising head of bed, avoiding meals within 3 hour of bed time , weight loss).[9] Drug therapy includes antacid, proton pump inhibitor, H2 receptor antagonist ,GABA b agonists (baclofen). Surgical treatment include fundoplication. In this study we are using drug therapy i.e. pantoprazole and baclofen.

Pantoprazole is the prototype member of substituted benzimidazoles which inhibit the final common step in gastric acid secretion. The only significant pharmacological action of pantoprazole is dose dependent suppression of gastric acid secretion.

Pantoprazole is inactive at neutral pH, but at pH < 5 it rearranges to two charged cationic forms (a sulphenic acid and a sulphenamide configurations) that react covalently with SH groups of the H+K+ATPase enzyme (in the parietal cell) and inactivate it irreversibly, especially when two molecules of pantoprazole react with one molecule of the enzyme. After absorption into bloodstream and subsequent diffusion into the parietal cell, it gets concentrated in the acidic pH of the canaliculi because the charged forms generated there are unable to diffuse back. Moreover, it gets tightly bound to the enzyme by covalent bonds. These features and the specific localization of H+K+ATPase to the apical membrane of the parietal cells confer high degree of selectivity of action to pantoprazole. Acid secretion resumes only when new H+K+ATPase molecules are synthesized (reactivation half time 18 hours).[10] All proton pump inhibitors (PPIs) are administered orally in enteric coated form to protect them from molecular transformation in the acidic gastric juice. Pantoprazole available in oral and intravenous form. Oral bioavailability >50% due to acid lability. Pantoprazole should be taken in empty stomach, followed 1 hour later by a meal to activate the H+K+ ATPase and make it more susceptible to the Pantoprazole. Pantoprazole is highly plasma protein bound, rapidly metabolised in liver by CYP2C19 and CYP3A4 (plasma t½ ~1 hr). The metabolites are excreted in urine. No dose modification is required in elderly or in patients with renal/hepatic impairment.[10]

Baclofen- It is a skeletal muscle relaxant that works by inhibiting polysynaptic and monosynaptic afferent pathways at the level of the spinal cord. It is a derivative of gamma-aminobutyric acid (GABA) and stimulates GABA B receptors, leading to decreased excitatory input into alpha-motor neurons. TLESRs have been shown to be the main pathophysiological cause of reflux in patients suffering from GERD. Gamma-aminobutyric acid class B (GABA B) receptors play an important role in TLESRs and are found in neurons in the motor nucleus of the vagal nerve and nucleus tractus solitarius . Baclofen is a GABA B agonist, used as an add on therapy aimed at reducing the occurrence of TLESRs.[11]

MATERIALS AND METHODS

A hospital based Prospective study was done in the department of Department of Medicine at Guru Gobind Singh Medical College and Hospital, Faridkot after ethical permission. Total 60 patients of gastroesophageal reflux disease were selected on the basis of findings of upper GI endoscopy followed which gastroesophageal reflux scintigraphy was carried out on these patients and then cases with grade 3 gastroesophageal reflux disease were selected. Thereafter, these grade 3 gastroesophageal reflux disease patients were divided into 2 groups having 30 patients each. Group 1:- Patients of gastroesophageal reflux disease grade 3 were treated with pantoprazole (40mg) once daily. Group 2:- Patients of gastroesophageal reflux disease grade 3 were treated with combination of pantoprazole (40mg) once daily with baclofen(10mg) thrice daily.

INCLUSION CRITERIA
- Patients showing clinical features of gastroesophageal refluxdisease.
- Patients with age more than 18 years.
- Patients willing to take part in study.

EXCLUSION CRITERIA
- Patient's age less than 18 year
- History of any abdominal surgical intervention
- Patients in whom upper G I endoscopy was contraindicated.
- Patients in whom reflex scintigraphy was contraindicated.

METHODOLOGY
Patients were selected on the basis of inclusion and exclusion criteria. Written and informed consent were taken. Detailed history of patients with through clinical examination were taken. Laboratory Investigations such as Complete Blood Count, Renal Function Test, Liver function Test, Prothrombin Index, International Normalized Ratio, Viral markers (ELISA)- HBsAg, HCV HIV were done, Then we used FUJINON 530-WR video Upper Gastro-Intestinal Endoscope to select the cases of gastroesophageal reflux disease.

GRADING OF GASTROESOPHAGEAL REFLUX SCINTIGRAPHY
- GRADE 0- No visualization of tracer
- GRADE 1- Visualization of tracer in distal 1/3 of esophagus

- GRADE 2-Visualization of tracer in middle 1/3 of esophagus.
- GRADE 3-visualization of trace in proximal 1/3 of esophagus.

Grade 3 patients of GERD were selected and divided them into two groups Group 1 patients of gastroesophageal reflux disease treated with pantoprazole (40mg OD) and Group 2 patients of gastroesophageal reflux disease treated with combination of pantoprazole(40mg OD) with baclofen(10mg TDS) . After four week of treatment gastroesophageal reflux scintigraphy was repeated and result were analysed.

STATISTICAL ANALYSIS
Data was entered in MS Excel and analysis was done using SPSS version. Data was presented as mean and standard deviation for continuous variables and as percentages for categorical variables. Unpaired t test was done to compare two groups means. Chi-square test was done to find out association between categorical variables. P value of less than 0.05 was considered as statistically significant.

RESULTS
The present study was done at Department of Medicine and Department of Nuclear Medicine, Guru Gobind Singh Medical College and Hospital Faridkot. 60 patients with grade 3 GERD selected afterGR scintigraphy were included in this study.

TABLE 1: Gender Distribution in GERD patients

Gender	Frequency	Percentage
MALE	27	45.0
FEMALE	33	55.0
Total	60	100.0

Out of total 60 patients who presented with GERD, 27 (45%) were male and 33 (55%) were female. (Table 1).

TABLE 2: Frequency of GERD in different age groups

Age group	Frequency	Percentage
18-30	13	21.7
31-40	12	20.0
41-50	19	31.7
51-60	7	11.7
61-70	6	10.0
71-80	3	5.0
Total	60	100.0
MEAN±SD (RANGE)	44.67±16.0 (18-80)	

Table 2 shows that higher frequency of occurrence of GERD was in the age group 41-50 years with mean age 44.67±16.0 years. GERD was more in patients with BMI between 18.5-24.9. 32 patients (53.3%) had BMI between 18.5-24.9, followed by 26 patients (43.3%) in 25-29.9 group and 2(3.3%) patients were in <18.5 group.

TABLE 3: Base line frequency of symptoms in GERD patients

Clinical features	Frequency	Percentage
Heart Burn	49	81.7
Regurgitation	47	78.3

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Chest Pain	21	35.0
Hoarseness	8	13.3

The above table shows that frequency of occurrence of heart burn, regurgitation, chest pain and hoarseness in patients of GERD before treatment was 49(81.7%), 47(78.3%), 21(35%) and 8 (13.3%) respectively.

TABLE 4: Frequency of symptoms in GERD patients after treatment

Clinical features- aftertreatment	Frequency	Percentage
Heart Burn	10	16.7
Regurgitation	12	20.0
Chest Pain	4	6.7
Hoarseness	2	3.3

Table 4 shows that there was difference in frequency of symptoms after the treatment. Frequency of Heart burn was 10(16.7%), Regurgitation was 12(20%), Chest pain was 4(6.7%) and Hoarseness was 2(3.3%).

TABLE 5: Frequency of grading of GERD after treatment in total patients

Grade of GERD	Frequency	Percentage
GRADE 0	16	26.7
GRADE 1	25	41.7
GRADE 2	18	30.0
GRADE 3	1	1.7
Total	60	100.0

Table 5 depicts that 25(41.7%) cases belonged to grade 1, 18(30.0%) cases belong to grade 2, 16(26.7%) cases belonged to grade 0 and 1(1.7%) cases belonged to grade 3 after treatment. Mean age in group 1 was 42.6 ±12.6 and group 2 was 46.8 ±18.8. Mean BMI was 24.6 ±1.7 in group 1 and 24.2 ±2.3 in group 2. Group 1 had 43.3% males and 56.7% females and group 2 had 46.7% males and 53.3% females. Group 1- 90% cases and in group 2- 73.3% cases had heart burn, (before treatment). In our study we observed that the symptoms of Heart Burn improved after treatment in group 2 - 1(3.3%) as compared to group 1 - 9(30%) , this was statistically significant (p = 0.006).

TABLE 6: Frequency of Regurgitation in study groups(before treatment)

	Drug			
	Group 1		Group 2	
Regurgitation	N	%	N	%
PRESENT	26	86.7%	21	70.0%
ABSENT	4	13.3%	9	30.0%
TOTAL	30	100.0%	30	100.0%

The above table shows group 1- 86.7% cases and in group 2- 70.0% cases had Regurgitation (before treatment).

TABLE 7: Frequency of Regurgitation in study groups after treatment

	Drug				Chi squaretest
	Group 1		Group 2		
Regurgitation	N	%	N	%	P value
PRESENT	11	36.70%	1	3.30%	
ABSENT	19	63.33%	29	96.70%	0.001
TOTAL	30	100.0%	30	100.0%	

In this study we observe that there was significant improvement noted in Regurgitation after treatment in group 1 -19(66.33%) and group 2- 29(96.7%), with significant p value (p = 0.001). In group 1- 33.3% cases and in group 2- 36.7% cases had chest pain (before treatment). There was non-significant (p=0.301) difference noted in complain of Chest Pain after treatment, in group 1-[3(10%) cases] and group 2 – [1(3.3%) cases]. The above table shows in group 1- 13.3% cases and group 2- 13.3% cases presented with hoarseness of voice (before treatment). There was non- significant (p=0.150) difference noted in complain of Hoarseness of voice after treatment, between in group 1 and group 2.

TABLE 8: Comparison in symptoms recovery after therapy in study groups

	Drug				Chi square test
	Group 1		Group 2		
Changes in symptomsafter treatment	N	%	N	%	P value

	RECOVERED	18	66.7%	21	95.5%	
HEART BURN(N=49)	NOT RECOVERED	9	33.3%	1	4.5%	0.013
	RECOVERED	15	57.7%	20	95.2%	
REGURGITATION(N=47)	NOT RECOVERED	11	42.3%	1	4.8%	0.003
	RECOVERED	7	70.0%	10	90.9	
CHEST PAIN(N=21)	NOT RECOVERED	3	30.0%	1	9.1%	0.223
	RECOVERED	2	50.0%	4	100.0%	
HOARSENESS OFVOICE (N=8)	NOT RECOVERED	2	50.0%	0	0.0%	0.102

Table 9 shown that the patients of GERD, heart burn improved in 66.7% patients in group 1 and 95.5% patients in group 2 with significant p value (p=0.013), regurgitation improved in 57.7% in group 1 and 95.2% patients in group 2 with significant p value (p= 0.003), chest pain improved in 70% in group 1 and 90% in group 2 with non-significant p value (p = 0.223) and hoarseness of voice improved in 50% in group 1 and 100% in group 2 with non-significant p value (p = 0.102).

TABLE 9: Improvement in grading of GERD after treatment in study groups

GERD grade	Drug				Chi squaretest
	Group 1		Group 2		
	N	%	N	%	P value
GRADE 0	0	0.0%	16	53.3%	
GRADE 1	13	43.3%	12	40.0%	
GRADE 2	16	53.3%	2	6.7%	
GRADE 3	1	3.3%	0	0.0%	
TOTAL	30	100.0%	30	100.0%	<0.001

In group 1, grade 2 GERD was observed in 53.3% cases followed by grade 1 in 43.3%. Whereas in group 2, grade zero was seen in 53.3% cases followed by grade 1 in 40%. This observation was statistically significant (p<0.001).

TABLE 10: Relationship between grading of GERD and BMI after therapy

		BMI						Chi square test
		<18.5		18.5-24.9		25-29.9		
		N	%	N	%	N	%	P value
GERD GRADE	GRADE0	1	50.0%	10	31.3%	5	19.2%	
	GRADE1	0	0.0%	12	37.5%	13	50.0%	
	GRADE2	1	50.0%	9	28.1%	8	30.8%	
	GRADE3	0	0.0%	1	3.1%	0	0.0%	
	Total	2	100.0%	32	100.0%	26	100.0%	0.706

Table No. 10 shows that, after therapy in patients with BMI<18.5, 50% had grade 0 GERD, 50% had grade 2 GERD. Among patents with BMI 18.5-24.9, 31.3% had grade 0, 37.5% had grade 1, 28.1% with grade 2 and 3.1% had grade 3 GERD. In patients with BMI 25-29.9, 19.2% had grade 0, 50% had grade 1, 30.8% had grade 2 GERD. Relationship between GERD and BMI was found to be not significant (p=0.706)

DISCUSSION
GERD is the most common gastrointestinal disease. It is associated with a huge economic burden and decreased quality of life. GERD is defined as symptoms or complications arising from the reflux of gastric contents into the esophagus and oral cavity. In our study, total 60 patients of GERD grade 3 were taken which were divided into two groups and were compared on the basis of treatment given i.e., group 1 pantoprazole and group 2 pantoprazole with baclofen. In this study, mean age of the patients in group 1 was 42.60±12.6 years and in group 2 was 46.8±18.8 years. In a similar study conducted by Abbasinazari et al, the mean age of subjects was 41.0 ±14.5 years in SR baclofen group and 36.8±9.0 years in placebo group.[12] Another study conducted by Lee J Y et al showed that mean age in esmoprazole plus mosapride group was 54.9±11.1 years and in esmoprazole group was 55.8±8.4 years.[13]

Also in our study, females were affected more than males in both group 1 (43.3% males and 56.7% females) and group 2 (46.7% males and 53.3% females). In the study done by Santeerapharp A et al it was found that group 1(Omeprazole with baclofen)

was having 42.9% males and 56.3% females and group 2 (Omeprazole with placebo) included 57.1% males and 43.8% females.[14]

Our study assessed the relationship of demographic parameters in causing GERD. BMI as a risk factor in causing GERD symptoms was assessed in between two groups. Our study showed that most of the patients in group 1 had BMI 24.6±1.7 and patients in group 2 had BMI 24.2±2.3. So in our study, BMI did not have prominent role in causing GERD symptoms. Another study by Santeerapharp A et al showed baclofen group had BMI between 25.41±5.45 and placebo group had BMI 25.25±4.15 and p value 0.93 was not significant.14 In study conducted by Marakhouski KY et al, it was found that OMZ plus DSR group had BMI 28.2±4.7 and OMZ group had BMI between 25.9±4and the difference was not significant.[15]

We also compared the prevalence of common symptoms of GERD before treatment and it was found that prevalence of heartburn in group 1 was 27 (90%) and group 2- 22 (73%) followed by acid regurgitation in group 1 -26 (86.7%), group 2 -21 (70%) and chest pain in group 1 -10 (33.3%) and group 2- 11 (36.6%) in decreasing order respectively. Similar study done by Wang HY et al, found that prevalence of common symptoms of GERD was heart burn 73.6%, acid regurgitation 81.9% and chest pain was 2.4%.16 Sharma PK et al in another study on GERD found that out of total subjects 71.1% had heart burn and regurgitation17 , 21% had only heart burn and 7.7% had only regurgitation . Another study done by Bhatia SJ et al on symptom profile of GERD patients and concluded that 77.6% had heart burn , 57.6% had regurgitation and 22.8% had chest pain.[3]

Our study also showed that the prevalence of heartburn after treatment in group 1- 9(30%), group 2- 1 (3.3%) (p=0.006); acid regurgitation in group 1 -11 (36.7%), group 2 -1 (3.3%)(p=0.001) and Chest pain in group 1 - 3 (10%), group 2- 1 (3.3%) (0.301). This data suggested that there was significant reduction in symptoms after treatment. Similar studies done by Abbasinazari M et al12 and Marakhouski KY et al15found that there was significant difference in prevalence of symptoms before and after treatment. Similar observations were also seen by Lee J Y. et al in their study done in 2017.[13]

In our study, reflux scintigraphy was performed on grade 3 GERD patients after treatment. It was found on scintigraphy that there was significant improvement in severity of GERD grading. After treatment there were 43.3% patients shifted to grade 1 GERD and 53.3% patients shifted to grade 2 GERD from grade 3 in group 1. There were 53.3% patients shifted to grade 0 GERD and 40% patients shifted to grade 1 GERD and 6.7% patients shifted to grade 2 from grade 3 in group 2 after treatment.

Puranik AD et. Al in their study also used Scintigraphic scoring system for grading severity of gastro-esophageal reflux. In this study analysis of before treatment scintigraphic scores had shown that most patients have a score of 8 or more, indicating that the majority of patients (71.8%) had moderate to severe GERD and post treatment scintigraphic scores had shown that most patients had a score of 5 or less i.e., about 77% indicating that post treatment there was effective reduction in the severity of GERD. In fact in 56.4% of patients, score was 0, which meant that there was no detectable GER post treatment.[18]

In our study, frequency of GERD symptoms were compared after treatment between group 1 and 2. Frequency of heart burn in group 1 was 9 (30%) and group 2- 1(3.3%) (p-value 0.006), frequency of acid regurgitation after treatment in group 1 was 11(36.7%) and group 2- 1(3.3%) (p = 0.001) and chest pain frequency after treatment in group1 was 3(10%) and group2 -1(3.3%) (p = 0.301). After analysis of this data, it was concluded that combination of pantoprazole with baclofen was more effective in reduction of GERD symptoms than pantoprazole alone.

A similar study done by Abbasinazaria M et al , evaluated symptoms of GERD after 2 weeks of treatment with omeprazole and baclofen. Analysis of the data indicated there was significant difference between the two groups in the prevalence of heartburn($p < 0.0001$) and regurgitation ($p < 0.0001$), whereas there is no significant difference in chest pain ($p = 0.35$) or hoarseness ($p = 0.93$). Statistical analysis revealed a significant difference in total GERD score ($p < 0.0001$) between the two groups. They concluded that group with omeprazole with baclofen regimen have significant improvement in GERD symptoms.[12]

Our study also compared the effect of pantoprazole with baclofen and pantoprazole alone in decreasing the severity of grading of GERD. It was found that there was significant difference in reduction of grading of GERD from grade 3 to grade 1 in group 1 (pantoprazole alone) and shifting of grading of GERD from grade 3 to grade 0 in group 2 (pantoprazole with baclofen). So it was concluded that pantoprazole with baclofen was more effective in decreasing the severity of grading of GERD.

CONCLUSION

In patients of Gastro-esophageal reflux disease, combination of pantoprazole with baclofen was more effective in treating these patients than pantoprazole alone. The improvement in symptoms as well as severity of GERD improved with combination of pantoprazole with baclofen as compared to pantoprazole alone.

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