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Efficacy and Safety of Fixed Dose Combination of Pantoprazole and Low Dose Amitriptyline in Indian Population Suffering From GERD with Co-Existing Anxiety

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Abstract

Aim: To evaluate the efficacy and tolerability of fixed dose combination of Amitriptyline and Pantoprazole in GERD (Gastroesophageal reflux disease) associated with anxiety.

Materials and Methods: A non-randomized, open labelled, non-comparative, multi-centric, study was conducted in total of 211 patients. Each patient was administered a fixed dose combination of Amitriptyline 10 mg and Pantoprazole 40 mg once a day, for 4 week. GERD questionnaire, HADS (Hospital Anxiety & Depression Score) & SF-8 questionnaire (Short Form Health Survey) were performed at baseline and at the end of study as assessment tools.

Results: At the end of study data was extractable only in 188 patients (132 males and 56 females, mean age was 44 ± 12 years). GERD symptoms & anxiety score reduced significantly ($p<0.0001$) at week 4 compared to baseline. SF-8 score also improved significantly ($p<0.0001$) at week 4. The coexistence of anxiety with GERD was observed more commonly in males compared to females. Tolerability of fixed dose combination was found to be good and none of the subjects discontinued the treatment.

Conclusion: Amitriptyline and Pantoprazole combination was found to be effective and safe for the management in those who had GERD with co-existing anxiety.

Keywords: GERD; Anxiety; Amitriptyline; Pantoprazole;

Introduction

Gastroesophageal reflux disease (GERD) is a condition characterized by the reflux of stomach contents into the esophagus, which causes several symptoms, such as heartburn and regurgitation. It is typically divided into three subtypes: reflux esophagitis (RE), nonerosive reflux disease (NERD) and Barrett's esophagus [1].

Presently, up to 70% of the patients with complaints of reflux symptoms have been noted to have NERD [2]. Despite the potency of proton pump inhibitors (PPIs) on gastric acid secretion, it is now evident that they do not suppress symptoms in patients with GERD as completely as was once supposed. Indeed, with the advent of more thorough symptom evaluation, it is now well recognized that both in the clinical study setting and in ordinary clinical practice, many GERD patients experience persistence of troublesome reflux symptoms while taking PPI therapy [3].

Some 40–50% of patients with NERD, and 6–15% of those with erosive esophagitis (EE), has been reported as refractory to PPI therapy [4].

According to the literature psychological factors, including anxiety and depression, play an essential role in the development of GERD and especially that of NERD [1].

One population based study showed that there is increase in GERD related symptoms due to presence of anxiety and depression [5].

In a recent study by Yang XY et al it was demonstrated that the presence of anxiety in NERD & RE was 49.66% & 44.03% respectively [1].

Predictions by many physicians and previous studies have established that patients with concurrent anxiety or depression would respond poorly to GERD treatment [6].

Thus, it has been proposed that patients who did not respond to PPI therapy are more likely to have psychosocial comorbidity than those who were successfully treated with a PPI [7].

Consequently, anti-anxiety medications may be alternative therapies for patients with NERD and RE if antacids cannot produce a satisfactory effect [1].

Materials and Methods

Design and Participants

This was a non-randomized, non-comparative, observational, multi-centric study to determine the effectiveness and safety of the fixed dose combination of Amitriptyline 10mg and Pantoprazole 40mg once daily for 4 weeks.

A total of 211 GERD patients (men and women, mean age: 44.16 ± 11.53 years) reporting to Gastroenterology OPD, were screened for the intensity of heartburn, regurgitation, retrosternal pain, nausea, sleep disturbance & use of additional medication on 4 point analog scale(0-3: 0=None; 1=Mild; 2=Moderate & 3=Severe). Evaluation of anxiety symptoms was done using hospital anxiety and depression scale (HADS) which was a 7-item self-rating questionnaire. Respondents had to indicate the frequency of any symptom on a four-point scale. Scores were calculated as the sum of their respective 7-item scores (ranging from 0 to 21) where (0-7 = normal, 8-10 = borderline abnormal, 11-21 = abnormal). Short-form health survey (SF-8) questionnaire consisting of 8 items was done on six- point scale (1-6: 1=Very Poor; 2=Poor; 3=Fair; 4=Good; 5=Very Good; 6=Excellent).

During the trial duration, patients were allowed to take additional medications like Levosulpiride, Domperidone, Antacids etc. for symptomatic relief.

Inclusion and Exclusion Criteria

GERD patients experiencing partial relief with PPI twice daily were included in the study. Total 211 patients with GERD & anxiety symptoms who gave their informed consent in the vernacular language were included in the study. Eligible patients were in the age range of 20-84 years and were diagnosed to have GERD with co-existing anxiety by utilizing GERD and HADS questionnaire at the baseline.

The exclusion criteria included patients with any of the several conditions listed as follows:

Use of prescribed non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin; a history of upper gastrointestinal surgery; comorbidities, such as scleroderma, diabetes mellitus, autonomic or peripheral neuropathy, myopathy, functional bowel disorder or any underlying disease (or medication) that might affect the lower esophageal sphincter pressure or increase the acid clearance time and inability or unwillingness to provide informed consent. Females who were pregnant or planning to conceive and lactating mothers were also excluded from the study.

Results

From total 211 patients included in the study, 23 were dropped out because they did not turn up to follow up at week 4, hence the data was extractable in total 188 patients. In this observational study we observed higher prevalence of GERD with co-existing anxiety in males compared to females (Figure 1).

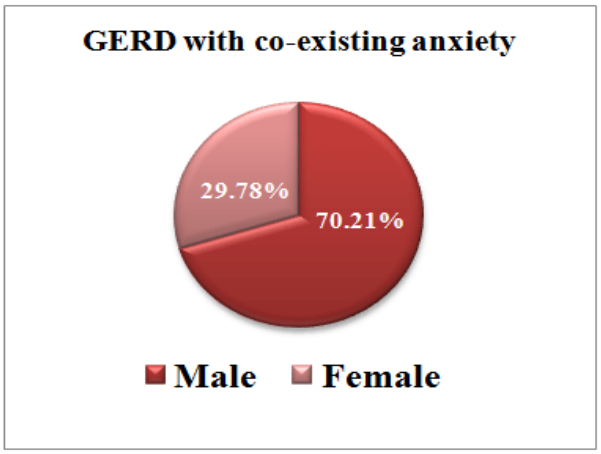

Figure 1: Prevalence of GERD with Co-existing anxiety

Evaluation of GERD symptoms using GERD questionnaire

The mean reduction in overall GERD symptoms was found to be clinically significant (*p Value <0.0001*) at week 4 compared to baseline (Figure 2). The mean change of individual symptom score using unpaired t-test is shown in Table 1.

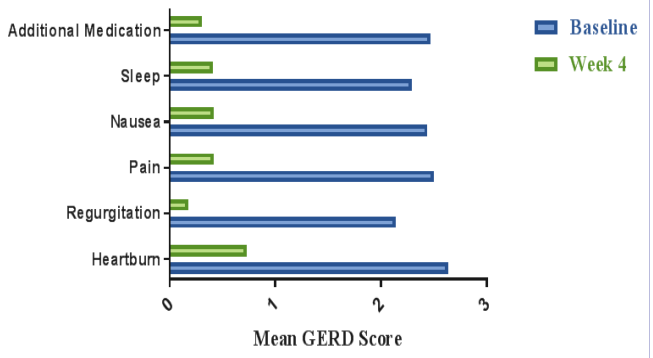

Figure 2: Improvement in GERD symptoms at Week 4

Anxiety Score

The change in anxiety score was statistically significant (p Value <0.0001) at week 4 compared to baseline (Figure 3). The mean change in anxiety score was performed using unpaired t-test and is described in Table 2.

Evaluation of physical and mental health using SF-8 Questionnaire

All parameters were found to be significantly (*p Value < 0.0001*) improved at week 4 when compared with baseline (Figure 4). Improvements in mean change of SF-8 questionnaire parameters at week 4 using unpaired t-test are presented in the Table 3.

The tolerability of this fixed dose combination was found to

Table 1: Evaluation of GERD Using GERD Questionnaire

Parameters	Baseline (Mean ± SEM)	Week4 (Mean ± SEM)	Mean Difference (95% Confidence Interval)	Percent Change (%)	p Value
Heartburn	2.638 ± 0.04179	0.7287 ± 0.03422	-1.91 ± 0.05401	72.37	*p < 0.0001*
Regurgitation	2.138 ± 0.05015	0.1755 ± 0.02882	-1.963 ± 0.05784	91.79	
Pain	2.5 ± 0.04619	0.4202 ± 0.03912	-2.08 ± 0.06053	83.19	
Nausea	2.441 ± 0.04898	0.4202 ± 0.03912	-2.021 ± 0.06269	82.78	
Sleep Disturbance	2.293 ± 0.04162	0.4096 ± 0.03751	-1.883 ± 0.05603	82.13	
Additional Medication	2.468 ± 0.04969	0.3085 ± 0.03621	-2.16 ± 0.06149	87.5	
SEM: standard error mean					

Table 2: Evaluation of Anxiety Using HADS Questionnaire

Parameter	Baseline (Mean±SEM)	Week 4 (Mean±SEM)	Mean Difference (95% Confidence Interval)	% Improvement	p Value
Anxiety Score	18.34 ± 0.2666	5.452 ± 0.1668	-13.97 ± 0.03132	70.27 %	*< 0.0001*
SEM: standard error mean					

Table 3: Evaluation of Physical and Mental Health using SF-8 Questionnaire

Parameters	Baseline (Mean ± SEM)	Week 4 (Mean ± SEM)	Mean Change (95% Confidence interval)	Percent Change (%)	p Value
General Health	3.564 ± 0.05848	4.064 ± 0.07528	0.5 ± 0.09533	14.02	*< 0.0001*
Physical functioning	3.58 ± 0.05838	4.415 ± 0.06524	0.8351 ± 0.08755	23.32	
Role Physical	3.58 ± 0.05838	4.415 ± 0.06524	0.8351 ± 0.08755	23.32	
Bodily pain	3.016 ± 0.0287	3.574 ± 0.06912	0.5585 ± 0.07484	18.5	
Vitality	2.963 ± 0.04291	3.729 ± 0.06601	0.766 ± 0.07873	25.82	
Social functioning	3.064 ± 0.04105	3.856 ± 0.06013	0.7926 ± 0.07281	25.84	
Role Emotional	2.931 ± 0.03377	3.745 ± 0.05688	0.8138 ± 0.06615	27.77	
Mental Health	3.005 ± 0.04365	3.723 ± 0.05784	0.7181 ± 0.07247	23.89	
SEM: standard error mean					

Table 4: Total No. of Adverse Events in 59 Patients

Sr. No	Adverse Events	Occurrence (%)
1	Vomiting	22 (11.7)
2	Drowsiness	18 (9.57)
3	Dryness of mouth	20 (10.63)
4	Weight gain	2 (1.06)
Total		62 (32.97)

be good, only 59 out of 188 (31.38%) patients reported to have adverse events (Table 4) of mild intensity which were self limiting and hence resolved on its own. None of the patients discontinued the treatment.

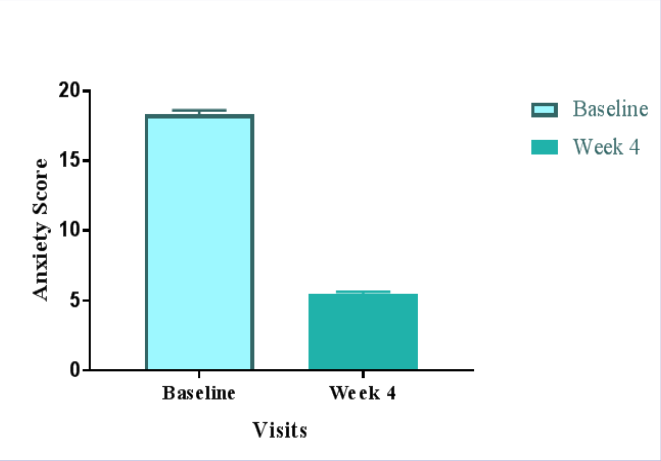

Figure 3: Improvement in anxiety score at Week 4

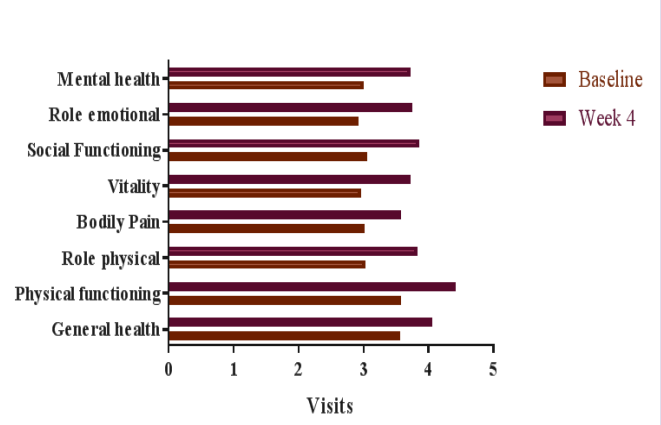

Figure 4: Improvement in SF-8 score at Week 4

Discussion

In our study we observed positive association between anxiety and GERD patients. Both GERD and anxiety were found to be significantly improved at week 4 in patients who were getting partial or no relief from PPI twice daily. Typical GERD symptoms such as heartburn and regurgitation were significantly ($p < 0.0001$) reduced by 72.37% & 91.79% respectively along with improvement in anxiety score by 70.27%. In addition to symptomatic improvement, in this study we found that there was significant improvement in QoL of patients assessed by SF-8 questionnaire. There was significant ($p < 0.0001$) improvement in general health, physical functioning, role physical, bodily pain, vitality, social functioning, role emotional and general health from baseline to week 4. The tolerability of this fixed dose combination was also found to be good as only 34.57% of patients observed to have mild intensity adverse events & there were no serious adverse events reported throughout the study duration. Reduction in intake of additional medication (Domperidone, Levosulpiride & Antacids) by 87.50% shows that the reported adverse events were self limited thus establishing an excellent tolerability and enhanced patient adherence for this combination.

Various studies evaluated the effect of stress on the gastrointestinal tract. More recent studies have focused on the relationship between stress and reported symptoms of GERD. Bradley et al. evaluated the relationship among stress, psychological traits associated with chronic anxiety, acid reflux parameters and perceptions of reflux symptoms [8]. Jansson et al reported that patients with anxiety but no depression had a 3.2-fold (95%CI: 2.7-3.8) increased risk of reflux symptoms [9]. Another significant finding was that reflux patients who were chronically anxious and exposed to prolonged stressful stimuli may be more likely to perceive low-intensity esophageal stimuli as painful reflux symptoms. Therefore, even normal esophageal acid exposure could trigger complaints of GERD symptoms. Also, it is not a specific psychiatric disorder that may be responsible for gastrointestinal distress but the presence of psychological distress predisposes the fact to have clinical manifestations of GERD [10].

Based on result of our study and the literature it can be postulated that anxiety plays a crucial role in precipitation & increase in GERD symptoms and subsequent reduction in quality of life of the patients. Hence consideration can be given to a low dose Amitriptyline in combination with Pantoprazole for the management of GERD with co-existing anxiety. Nonetheless this combination also has potential to reduce the PPI failure rate in patients with PPI refractory GERD which is particularly very common. Small duration and open label nature of the study were the only limitations, further long duration and double blind studies are warranted.

Conclusion

The fixed dose combination of Amitriptyline and Pantoprazole caused significant reduction in GERD symptoms along with improvement in anxiety & quality of life of the patients with good safety profile. This result justifies the presence of anxiety in patients suffering from GERD and it may have potential to reduce PPI failure rate in patients with PPI refractory GERD.

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