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Original Research Article

Comparison of safety and efficacy of pantoprazole alone with pantoprazole plus amitriptyline in functional dyspepsia patients: a randomized control trial

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ABSTRACT

Background: The term functional dyspepsia refers to ulcer-like symptoms in patients who lack overt gastro duodenal ulceration. Functional dyspepsia can be subdivided into: postprandial distress syndrome (PDS), epigastric pain syndrome (EPS), and based on the presence of symptoms related to meals. It is defined as the presence of one or more of the following: postprandial fullness, early satiation, epigastric pain or burning, and no evidence of structural disease. Pantoprazole alone is compared with pantoprazole plus amitriptyline to relieve dyspepsia symptoms in functional dyspepsia patients.
Methods: The study was a randomized, prospective, open label, comparative interventional study. The study was conducted in the Department of Pharmacology and Department of Gastroenterology and Hepatology at Dr. R.P.G.M.C. Kangra at Tanda Himachal Pradesh, India which is 700 bedded multispecialty tertiary health care from August 2023 to May 2024 and follow -up was done for 4 weeks after initiation of treatment, to compare the safety and efficacy of pantoprazole with pantoprazole plus amitriptyline in functional dyspepsia patients.
Results: In our study compared to pantoprazole group, pantoprazole plus amitriptyline group has statistically significant reduction in all the 3 scores *viz.* Glasgow dyspepsia severity score (GDSS) (4.26±1.14 versus 3.3±1.37, p=0.002), short form leads dyspepsia questionnaire (SF-LDQ) (4 [3-5] versus 3 [2-4], p=0.005), and visual analogue pain score (VAS) (1 [1-2] versus 1 [0-1], p=0.0009).
Conclusions: The combination of pantoprazole and amitriptyline was more effective than pantoprazole alone in improving symptoms of functional dyspepsia, with no significant safety concerns.

Keywords: Amitriptyline, Glassgow dyspepsia severity score, Pantoprazole, Visual analog scale

INTRODUCTION

Dyspepsia describes symptoms such as epigastric discomfort, bloating and nausea, which are thought to originate from the upper gastrointestinal tract.[1] Dyspepsia was originally defined as any symptoms referable to the upper gastrointestinal tract.[2] The Rome committee has developed iterative definitions of dyspepsia that have become more specific culminating in Rome IV.[3]

These definitions have attempted to minimize the inclusion of gastro-esophageal reflux disease in those with dyspepsia by excluding patients with heartburn and acid regurgitation.[4]

The Rome Foundation classification of functional gastrointestinal disorders (FGIDs) is based primarily on symptoms rather than physiological criteria.[5] Functional gastrointestinal (GI) disorders are disorders of gut–brain interaction. It is a group of disorders classified by GI

symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota and altered central nervous system (CNS) processing.[6]

The term functional dyspepsia refers to ulcer-like symptoms in patients who lack overt gastro duodenal ulceration. Functional dyspepsia can be subdivided into: postprandial distress syndrome (PDS), and epigastric pain syndrome (EPS). Based on the presence of symptoms related to meals. It is defined as the presence of one or more of the following: postprandial fullness, early satiation, epigastric pain or burning, and no evidence of structural disease.[7]

International gastroenterology surveillance study (DIGEST); a survey of over 5500 persons showed that around one third of the normal persons interviewed reported dyspeptic symptoms, including acute dyspepsia in 6.5% and chronic dyspepsia in 22.5% of cases. Only in 10 to 25% is the social impact of their symptoms great enough for them to consult a physician.[8] Only 20% of patients with functional dyspepsia ever become free of symptoms in the long term.[9,10]

Functional dyspepsia has been considered an idiopathic disorder, but this view is changing. In some cases, functional dyspepsia develops after acute infectious gastroenteritis, suggesting acute intestinal inflammation may play a role.

A typical history of long-standing troublesome early satiety and postprandial fullness is sufficient to make a clinical diagnosis and commence treatment, but often gastroscopy is required. Any of the following red flag symptoms should prompt endoscopy: new onset in older age, unintended weight loss, vomiting, bleeding, iron deficiency anemia, family history of upper gastrointestinal cancer, and progressive dysphagia or odynophagia. It is otherwise reasonable to screen for *H. pylori* infection by breath or stool antigen test and treat positive cases.[9]

Treatment is offered with the aim of improving symptoms, social functioning, and quality of life is vital. Although there is little evidence that lifestyle changes lead to symptom improvement, a recent small RCT of aerobic exercise, in addition to conventional management, demonstrated a significant benefit on dyspepsia symptoms, compared with conventional management alone.[11] Conventional therapies for acid peptic disease was proton pump inhibitor (pantoprazole). As functional dyspepsia involves gut brain interaction so combination therapy of pantoprazole and amitriptyline a tricyclic antidepressant was found to be better in efficacy than pantoprazole alone.

METHODS

The study was randomized, prospective, open label, comparative interventional study, conducted in the Department of Pharmacology and the Department of Gastroenterology and Hepatology at Dr. R.P.G.M.C. Kangra at Tanda, India which is 700 bedded multispecialty tertiary health care institution.

Inclusion criteria

All the consenting adult patients of age 18 to 75 years, of either gender with no evidence of structural disease on upper gastro-intestinal endoscopy that is likely to explain the symptoms.

Exclusion criteria

Patients not willing to give written informed consent, pregnant & lactating females, active alcohol users, patients allergic or with known contraindications to any of study drugs, known patient of cirrhosis, chronic kidney disease, chronic heart failure, coronary artery disease, contraindications of amitriptyline, such as prostatic disease, glaucoma, history of seizure, retention of urine, use of similar drugs during the last 2 weeks.

Study duration

The enrolment was done after registration with Clinical Trial Registry-India (CTRI) vide number CTRI/2023/07/055175 from August 2023 to May 2024 and follow-up was done for 4 weeks after initiation of treatment.

Study intervention

All patients of un-investigated dyspepsia who came to Gastroenterology out-patient department were subjected to upper GI endoscopy (UGIE) and ultrasonography (USG) abdomen (whenever indicated). UGIE was done with the help of gastroscope from Karl Storz SE and Co. KG, model no. 13821 PKS, as available in the department of Gastroenterology and Hepatology of Dr. R.P.G.M.C. Kangra at Tanda, Himachal Pradesh, India. Patient were subjected for *H. pylori* testing by stool antigen test or by gastric antrum biopsy histopathological examination, before labelling them as functional dyspepsia. Patients in whom there was no evidence of any structural disease/organic dyspepsia and were fulfilling the criteria for functional dyspepsia were included in the study after making them go through and understand the patient information sheet thoroughly regarding the study and related aspects.

After a written informed consent, the participants were assigned to one group either A or B, based on computer generated random numbers.

Before initiating the treatment baseline haemoglobin (Hb), total leukocyte count (TLC), fasting blood sugar (FBS), serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), serum urea, serum creatinine and serum electrolytes were done and

these investigations were repeated after completion of 4 weeks of treatment.

The group A participants took pantoprazole 40 mg with water, 30 minutes before breakfast (BBF) per oral for 4 weeks.

The group B participants took pantoprazole 40 mg BBF + amitriptyline 10 mg at bedtime (hs) per oral with water for 4 weeks.

Patients were contacted telephonically on the next day of initiating the therapy and enquired for any discomfort or side effects.

Measurement of outcome

For measurement a series of questionnaires including the short form Glasgow dyspepsia severity score (GDSS), short form leeds dyspepsia questionnaire (SFLDQ) and visual analog scale (VAS) for pain assessment will be completed by the patients before treatment and at 4 weeks after treatment.

On completion of 4 weeks of intervention the outcome was assessed on the basis of - safety in which all the adverse events that occurred in subjects during study period were noted, and efficacy which was evaluated by decrease in GDSS score, decrease in SFLDQ score, and decrease in VAS score.

RESULTS

The data collected was tabulated in Microsoft excel and analysed for various parameters. The data entry was done in the Microsoft excel spreadsheet and the final analysis was done with the use of statistical package for social sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 25.0. Quantitative data was presented as mean±standard deviation (mean±SD). Student's t-test was used for comparing continuous variables between the two groups. Chi square or Fisher's exact probability test was used for comparing the qualitative data between the two groups. P value <0.05 was measured as statistically significant.

A total of 74 patients of age 18 to 75 years with no evidence of structural disease were included in the study and were randomly divided into two groups:

In the pantoprazole group (n=36), participants were given pantoprazole 40 mg, 30 minutes before breakfast (BBF) per oral for 4 weeks. Two patients lost to follow-up (patients refused to continue in the study and was unwilling to follow the medication).

In the pantoprazole plus amitriptyline group (n=38), participants were given pantoprazole 40 mg, BBF + amitriptyline 10 mg at bedtime (hs) per oral for 4 weeks. One patient lost to follow-up (patients refused to continue in the study and was unwilling to follow the medication).

Baseline and demographic parameters

Baseline and demographic parameters were comparable in both the groups in this study.

Age

The mean ± standard deviation (SD) age in the pantoprazole only group was 45.38±15.31, and in the pantoprazole plus amitriptyline group, it was 47.27±15.26, with no significant difference between them (p=0.605).

Gender

In our study pantoprazole only, group compared to pantoprazole plus amitriptyline group had similar gender distribution (female: 52.94% versus 59.46%, male: 47.06% versus 40.54%) (p=0.58).

Table 1 shows gender-wise distribution of patients between two groups in which ECG was WNL for all patients in both the groups, UGIE was normal for all patients in both the groups, and *H. pylori* was negative for all patients in both the groups.

Mean±SD of improvement (%) in pantoprazole plus amitriptyline group was 66.51±11.72 which was significantly higher as compared to pantoprazole only group (58.28±8.91) (p value=0.001).

Blood biochemistry

Baseline laboratory parameters namely; haemoglobin (Hb), total leukocyte count (TLC), fasting blood sugar (FBS), serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), serum urea, serum creatinine and serum electrolytes were comparable between two groups.

Pre-treatment and post-treatment laboratory parameters were comparable in terms of haemoglobin (Hb), total leukocyte count (TLC), fasting blood sugar (FBS), serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), serum urea, serum creatinine and serum electrolytes. This observation suggests that both drugs are safe in the given population. Tables 2-4 shows comparison of various blood biochemical parameters.

Efficacy

Dyspepsia severity measurement scores

Glassgow dyspepsia severity score

In our study both the groups had comparable GDSS scores before initiating the treatment (9.44±2.13 versus

9.41±2.03, p=0.943). However, after treatment, GDSS (4.26±1.14 versus 3.3±1.37, p=0.002) was significantly different between the two groups with significantly lower GDSS in pantoprazole plus amitriptyline group. Within each group, there was a significant reduction in GDSS after treatment (p<0.0001 for both groups). Figure 1 shows comparison of GDSS between two groups.

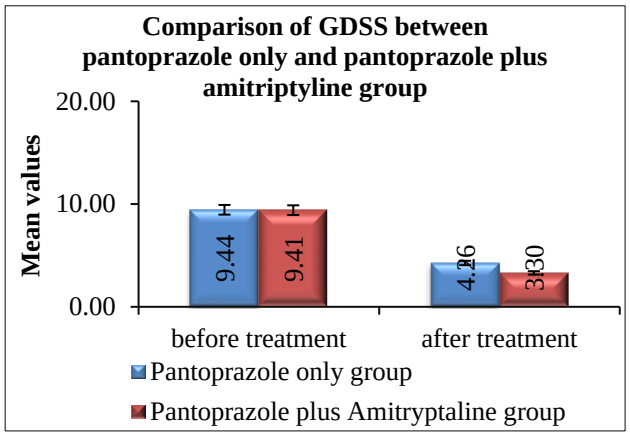

Figure 1: Comparison of GDSS between two groups.

Short form leads dyspepsia questionnaire

In our study both the groups had comparable SF-LDQ scores before treatment (10 [7.25-14] versus 9 [8-12], p=0.481). However, after treatment, SF-LDQ (4 [3-5] versus 3 [2-4], p=0.005) was significantly different between the two groups with significantly lower in pantoprazole plus amitriptyline group. Within each group, there was a significant reduction in SF-LDQ after treatment (p<0.0001 for both groups). Figure 2 shows comparison of SF-LDQ between two groups.

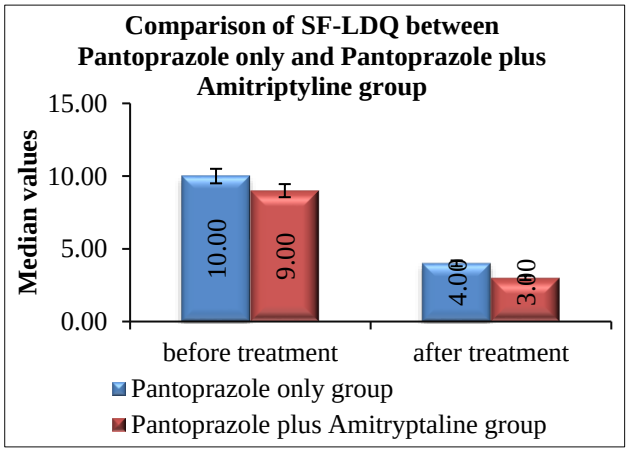

Figure 2: Comparison of SF-LDQ between two groups.

Visual analogue scale

In our study both the groups had comparable VAS scores before treatment (4 [4-5] versus 4 [4-4], p=0.157. After treatment, VAS scores (1 [1-2] versus 1 [0-1], p=0.0009) were significantly different between the two groups with significantly lower in pantoprazole plus amitriptyline group. Within each group, there was a significant reduction in VAS scores after treatment (p<0.0001 for both groups). Figure 3 shows comparison of VAS score between two groups.

Table 1: Gender-wise distribution of patients between two groups.

Gender	Pantoprazole only group (n=34) (%)	Pantoprazole plus amitriptyline group (n=37) (%)	Total (%)	P value
Female	18 (52.94)	22 (59.46)	40 (56.34)	0.58†
Male	16 (47.06)	15 (40.54)	31 (43.66)	
Total	34 (100)	37 (100)	71 (100)	

† Chi square test

Table 2: Comparison of haemoglobin and TLC levels between two groups.

Blood parameters	Pantoprazole only group (n=34)	Pantoprazole plus amitriptyline group (n=37)	Total	P value
Haemoglobin (g/dl)				
Mean±SD	12.62±1.47	12.15±1.36	12.38±1.42	0.167‡
Median (25^{th}-75^{th} percentile)	12.8 (12-13.6)	12.4 (11.2-13)	12.6 (11.3-13.4)	
Range	9.4-15.2	9.4-14.6	9.4-15.2	
Total leucocyte count (cells/mm^3)				
Mean±SD	6691.18±814.4	6683.78±819.73	6687.32±811.34	0.97‡
Median (25^{th}-75^{th} percentile)	6600 (6250-7000)	6500 (6200-7000)	6600 (6200-7000)	
Range	5100-10000	5100-10000	5100-10000	

‡ Independent t test

Table 3: Comparison of fasting blood sugar (mg/dl) between two groups.

Fasting blood sugar (mg/dl)	Pantoprazole only group (n=34)	Pantoprazole plus amitriptyline group (n=37)	Total	P value
Mean±SD	83.68±8.55	83.24±8.8	83.45±8.62	0.834‡
Median (25th-75th percentile)	84 (78-90)	84 (78-90)	84 (78-90)	
Range	70-98	69-98	69-98	

‡ Independent t test

Table 4: Comparison of LFT and RFT parameters between two groups.

Parameters	Pantoprazole only group (n=34)	Pantoprazole plus amitriptyline group (n=37)	Total	P value
SGOT (IU/l)				
Mean±SD	26.68±10.43	27.14±10.23	26.92±10.26	0.852‡
Median (25th-75th percentile)	25.5 (18-32.75)	26 (18-34)	26 (18-34)	
Range	14-49	14-49	14-49	
SGPT (IU/l)				
Mean±SD	20.65±8.4	20.38±7.71	20.51±7.99	0.889‡
Median (25th-75th percentile)	18 (14-27.75)	20 (12-27)	18 (13-27)	
Range	10-42	10-37	10-42	
Serum urea (mg/dl)				
Mean±SD	16.24±5.66	15.95±5.25	16.08±5.41	0.824‡
Median (25th-75th percentile)	16.5 (12-21.5)	15 (12-20)	15 (12-20)	
Range	6-25	6-25	6-25	
Serum creatinine (mg/dl)				
Mean±SD	0.73±0.17	0.73±0.15	0.73±0.16	0.982‡
Median (25th-75th percentile)	0.72 (0.62-0.868)	0.72 (0.62-0.89)	0.72 (0.62-0.89)	
Range	0.4-1.06	0.4-1.06	0.4-1.06	

‡ Independent t test

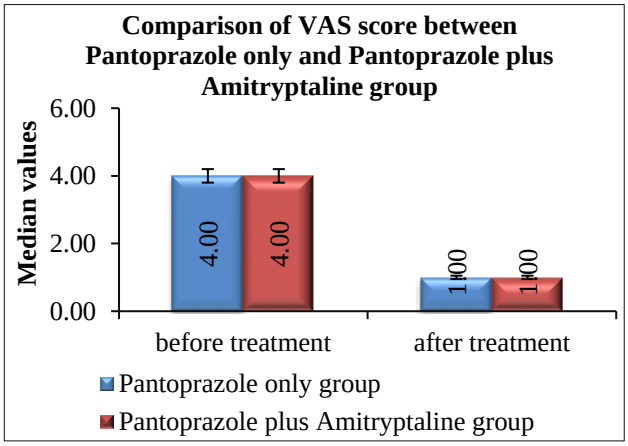

Figure 3: Comparison of VAS score between two groups.

DISCUSSION

The aim of our study was to evaluate the efficacy and safety of pantoprazole alone and pantoprazole with amitriptyline in treatment of functional dyspepsia patients. The results demonstrated that the addition of amitriptyline significantly improved patient outcomes, as evidenced by a greater reduction in dyspepsia severity scores across multiple assessment tools (GDSS, SF-LDQ, and VAS) compared to pantoprazole alone.

Interpretation of results

Efficacy comparison

The mean improvement in dyspepsia severity measured by GDSS was significantly higher in the pantoprazole plus amitriptyline group (66.51±11.72) compared to the pantoprazole-only group (58.28±8.91), with a p value of 0.001 indicating strong statistical significance. This aligns with findings from previous studies, such as the randomized controlled trial conducted by Liu et al, which reported a higher response rate for amitriptyline (53%) compared to pantoprazole (38%) in similar patient populations.[12] The current study's results support the hypothesis that combining a proton pump inhibitor with an antidepressant can yield superior therapeutic outcomes for functional dyspepsia.

Demographic and baseline comparisons

Demographic parameters, including age and gender distribution, were comparable between both groups, which strengthens the validity of the findings as they suggest that observed differences in outcomes are likely due to

treatment rather than demographic variations. The mean age was similar across groups (45.38±15.31 for pantoprazole only and 47.27±15.26 for the combination group), and gender distribution did not differ significantly (p=0.58).

In the randomized controlled trial (RCT) done by Liu et al in 2020 comparison of amitriptyline and pantoprazole was done in treatment of functional dyspepsia. Mean age in amitriptyline plus pantoprazole group was 41±11.50 and 41.29±10.84 in pantoprazole group with no significant difference between them (p=0.964).[12]

Safety profile

Both treatment regimens showed a favorable safety profile, as baseline laboratory parameters remained comparable post-treatment. This observation is consistent with findings that proton pump inhibitors, including pantoprazole, are generally safe and well-tolerated. Moreover, the combination of amitriptyline and pantoprazole has been shown to be effective and safe for managing gastroesophageal reflux disease (GERD) associated with anxiety, further supporting the safety of this combination therapy.[13]

Comparison with previous studies

The findings of this study are consistent with prior research that has highlighted the benefits of combining medications for treating functional dyspepsia. For instance, Liu et al's trial corroborated the enhanced efficacy of amitriptyline when used alongside pantoprazole.[13]

Ghosh and colleagues indicated the efficiency of a fixed-dose combination (FDC) of rabeprazole and itopride [a prokinetic (PK) agent] in the management of FD [Ghosh et al. 2008]. The results indicated that most patients experienced symptom relief, with 93% reporting an excellent or good response to treatment.[14]

Moreover, studies have shown that morning administration of pantoprazole optimizes its efficacy due to its pharmacokinetic properties, which may further enhance symptom relief when combined with amitriptyline.[12] This suggests that timing and combination therapy could be critical factors in improving treatment outcomes for patients suffering from functional dyspepsia.

Mechanism of action

Previous studies have demonstrated the efficacy of tricyclic antidepressants like amitriptyline in the management of functional dyspepsia. The proposed mechanisms include effects on central pain modulation, gastric accommodation, and visceral hypersensitivity, likely mediated through amitriptyline's antagonism of serotonin, histamine, and norepinephrine receptors.

These findings help interpret the superior symptomatic improvement seen with the combination of pantoprazole and amitriptyline compared to pantoprazole alone in the current study.

Importance of effective treatment

Studies have highlighted the significant economic burden and impaired quality of life associated with functional dyspepsia, emphasizing the need for effective treatment options like the combination therapy evaluated in this study.

Establishing an effective doctor-patient relationship and a shared understanding in the management of functional dyspepsia has also been shown to reduce healthcare utilization and improve quality of life.

Limitations

As the study being postgraduate thesis, patient recruitment was done for limited period. Hence small sample size is the major limitation of this study. We administered 40 mg of pantoprazole and amitriptyline (10 mg) at a low dose for four weeks. Varying the dosage and duration may result in greater improvement.

CONCLUSION

The combination of pantoprazole and amitriptyline was more effective than pantoprazole alone in improving symptoms of functional dyspepsia, with no significant safety concerns. These findings suggest the combination therapy should be considered as a first-line treatment option for functional dyspepsia patients, although further validation in larger studies is needed.

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