



Science

**A PROSPECTIVE STUDY INVOLVING COMPARISON OF
ACOTIAMIDE WITH RABEPRAZOLE VS. DOUBLE DOSE
RABEPRAZOLE IN PATIENTS HAVING OVERLAPPING SYMPTOMS
OF PROTON PUMP INHIBITOR REFRACTORY
GASTROESOPHAGEAL REFLUX DISEASE AND FUNCTIONAL
DYSPEPSIA**

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Abstract

Introduction: Gastroesophageal reflux disease (GERD) is a digestive disorder that affects the lower esophageal sphincter (LES). Functional dyspepsia (FD) is characterized by troublesome early satiety, epigastralgia or heart burn. It is often overlooked as the symptoms overlap with GERD. This study aims to compare the effectiveness of Acotiamide+Rabeprazole vs. a double dose of Rabeprazole in Indian population.

Method: In this study 60 patients diagnosed with PPI refractory GERD (taking PPI>8weeks) and FD with no gastric or duodenal organic abnormalities were randomly allocated in two groups. Group 1 received a combination of Acotiamide (200mg/day) +Rabeprazole (20mg/day) and group 2 received a double dose of Rabeprazole (40mg/day). Follow ups were done every month for 3 consecutive months. The frequency and severity of symptoms were assessed using standard Izumo scale and FSSG scale.

Results: The total score and GERD score from the baseline were significantly reduced in group 1 however the reduction in FD score from baseline did not differ significantly in the two treatment groups according to F-scale. The proportion of patients with $\geq 50\%$ reduction in the total score for three upper gastrointestinal symptoms (heart burn, epigastralgia, and epigastric fullness) in the izumo scale was 96.7% in group 1 and 33.3% in group 2. Significant difference were noticed between the two groups. No serious adverse events were observed.

Conclusion: The combination group of Acotiamide+Rabeprazole was found to be more effective than double dose of Rabeprazole in reducing the overlapping symptoms of PPI refractory GERD and FD.

Keywords: Functional Dyspepsia (FD); PPI Refractory Gastroesophageal Reflux Disease (GERD); Proton Pump Inhibitor (PPI); Acotiamide, Rabeprazole; Izumo Scale; Frequency Scale for Symptoms of GERD (FSSG Scale).

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1. Introduction

Gastroesophageal reflux disease or GERD is a disorder of the GI tract which is characterized by episodes of reflux of gastric contents into the esophagus. In today's time the prevalence of GERD is increasing rapidly. Earlier increase in prevalence of GERD was mainly seen in geriatric patients due to polypharmacy, comorbid medical conditions etc. GERD is now commonly seen in young patients as well which may be due to etiologies like sedentary lifestyle, obesity, spicy food etc.[1] GERD is mainly of two types[2] - Reflux esophagitis classified into Grade A,B,C,D,M,N according to Los Angeles Classification[3] and Non erosive reflux disease(NERD). The characteristic symptoms of GERD are- heartburn, acid reflux, dysphagia and odonophagia. Extra esophageal symptoms include-chronic cough, asthma and laryngitis. Chronic GERD may lead to complications like Esophagitis, Baretts esophagus and cancer of the esophagus.[4]

The standard treatment of GERD mainly includes once daily dose of a Proton pump inhibitor(PPI).[5] Studies have found that about 30-40% of GERD patients reported either partial or complete lack of response of their symptoms to a standard PPI dose once daily leading to development of PPI REFRACTORY GERD.[6] The treatment of PPI refractory GERD includes either doubling the dose of current PPI or adding a new PPI. Symptoms of functional dyspepsia like troublesome early satiety, post prandial fullness (Post prandial distress syndrome –PDS) and epigastric pain (Epigastric pain syndrome –EPS) are found to be overlapping in patients with PPI refractory GERD. This makes diagnosis of PPI refractory GERD indistinguishable from FD.[7] These overlapping symptoms of PPI rectory GERD and functional dyspepsia significantly impairs patient's health related quality of life. In this study to treat overlapping symptoms of PPI refractory GERD and FD, a novel drug Acotiamide is used. Acotiamide is an acetylcholine esterase inhibitor. It acts by increasing production of acetylcholine, thereby improving gastrointestinal motility. Acotiamide is the world's first approved treatment for functional dyspepsia diagnosed by Rome III criteria, with its first approval occurring in Japan 2013 and manufactured by Zeria Pharmaceuticals[14] In India Acotiamide was first approved and manufactured in 2016 by Lupin Pharmaceuticals.[9] The primary objective of this study is to assess and evaluate the effectiveness of a combination of Acotiamide and Rabeprazole vs. Double dose Rabeprazole in patients by using Izumo and FSSG scoring system and to provide symptomatic relief in patients with PPI refractory GERD and FD. The secondary objective of this study is to improve the patient health related quality of life. In this study patients with symptoms of GERD overlapping with FD without any

gastric or duodenal abnormalities and patients taking PPIs for > 8 weeks with no reduction in symptoms whatsoever (PPI refractory) were selected.

2. Methods

Questionnaires: The reduction in symptoms of patients during every follow up were assessed using the Izumo scale and Frequency scale for symptoms of GERD (FSSG).

Izumo Scale was developed in Japan 2009 by Sato S, Furutak et.al. It was developed to determine the Quality of life and was published in the Japanese journal of gastroenterology. It is divided into 3 domains. Each domain comprises of three questions. Each question has a score of 0-5 indicating not bothered to intolerably bothered. The total score of each domain is 15. The three domains include questions on heartburn, epigastralgia and epigastric fullness respectively. Since FD includes EPS (epigastric pain syndrome) and PDS(post prandial distress syndrome) the dyspepsia score defined in the study is obtained by adding the EPS (Q 4-6, 0-15 points) and PDS (Q7-9, 0-15 points) =30 points. Higher the score higher the severity of symptoms. For GERD a domain score total of 4 or more points is considered a “significant symptom”. [10]

Fssg Scale or Frequency scale for symptoms of GERD is a questionnaire developed by “Kusano M. et al” in 2004 based on studies done in Japan. The study was conducted on 124 patients in the year 2004 with endoscopic findings of GERD. The frequency scale consists of questions of 12 highly ranked symptoms. Symptoms are ranked on a scale of 0-4. Higher the total score higher the frequency of GERD. Cut-off value is set at 8 points. [11]

Study Design: This is a single center comparative prospective study. Patients were randomly allocated in two groups based on the inclusion and exclusion criteria. The inclusion criteria comprises- both male and female patients above 18yrs of age; patients taking PPIs >8weeks; patients confirming at least one symptom in Izumo scale grading as “slightly bothered” or more for the GERD domain(heartburn, acid reflux and throat discomfort); patients confirming at least one symptom in Izumo scale as “slightly bothered” or more for the EPS domain(pain, burning sensation, early satiety); patients with GERD having grade M or higher as per the LA classification ; patients diagnostically confirmed of having FD with no signs of organic abnormalities(Liver, Gallbladder and pancreatic disorders) by Upper gastro intestinal endoscopy(UGIE)[8]. The exclusion criteria comprises- patients who do not comply to participate in the study; pediatrics and pregnant women; patients confirmed positive for H.pylori by rapid urease test; patients taking PPI< 8weeks; patients suffering with pancreatic and liver abnormalities; patients diagnosed with Irritable bowel syndrome(IBS); patients using proton pump inhibitor other than rabeprazole; patients under 18yrs of age. The study protocol was reviewed by the institutional review board of Deccan College of medical sciences. All the subjects were counselled about the aspects of the study and a written consent was obtained. Patients suffering with overlapping symptoms of GERD and FD despite taking PPI were assessed using the FSSG and Izumo questionnaire. Patients were randomized in two groups. Group 1 received Acotiamide (200mg/day) +Rabeprazole (20mg/day). Group 2 received double dose of Rabeprazole (40mg/day). Follow ups were done every month for 3 consecutive months starting from the baseline. Symptom scores were evaluated using Izumo and FSSG questionnaire before the start of treatment (0 visit) and followed during every visit. (Fig 1).

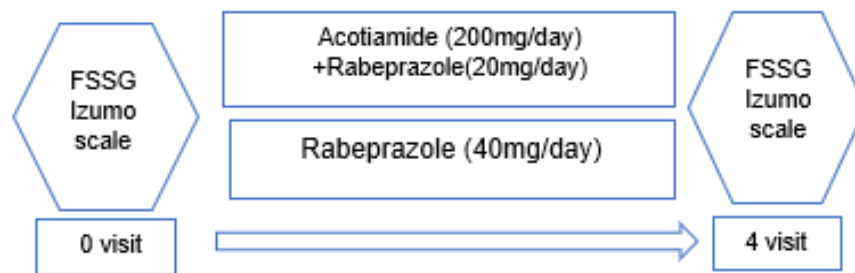


Figure 1:

3. Determination of Efficacy

The efficacy of the treatment modalities was compared using FSSG and Izumo questionnaire with focus on primary and secondary objectives.

- PRIMARY ENDPOINT- To compare the fraction of people having >50% reductions in symptoms (EPS, PDS and GERD) starting from the baseline towards the end of the treatment using Izumo scale.[8]
- SECONDARY ENDPOINT-
 - 1) Evaluation of FSSG scores for each symptom (FD and GERD score) and comparison of score between two treatment groups.
 - 2) Evaluation of Izumo scores for each symptom (heart burn, EPS and PDS score) and comparison of score between two treatment groups.
- EXPLORATORY ENDPOINT-
To determine the potential adverse effects of the drugs used in the study.
- SAMPLE SIZE- A total of 70 patients with PPI refractory GERD and FD despite treatment with standard dose of PPIs for more than 8weeks were included in the study. 10 patients were excluded after the detection of H.pylori infection. A sample size of 60 patients were randomly divided into 2 groups accounting to 30 patients in GROUP1 (combination therapy of Acotiamide(200mg/day)+ Rabeprazole 20mg/day) and 30 patients in GROUP 2(double dose of rabeprazole i.e 40mg/day).(Fig 2) The evaluation of symptoms was done by using a standard questionnaire- izumo scale and FSSG scale.

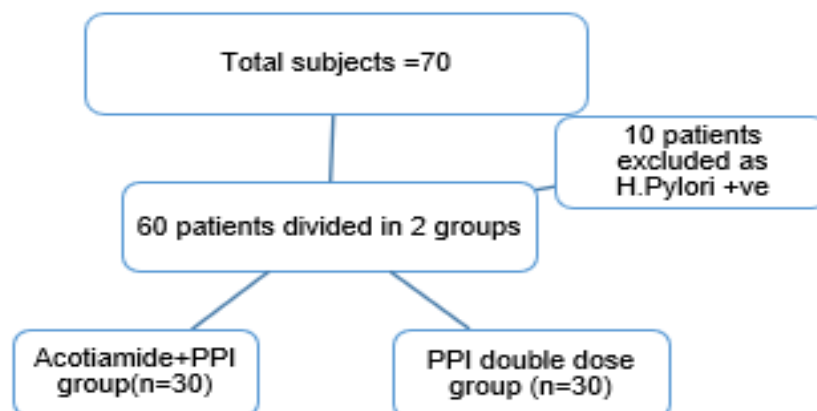


Figure 2:

4. Statistical Analysis

The efficacy was analyzed for all patients from the collected data. The clinical presentations of group1 and group 2 were compared using Fishers exact test and Mann Whitney test. The inter group changes in F scale and Izumo scale before and after the treatment were compared using Wilcoxon rank sum test. The analysis was performed using a graph Pad Prism software. A 5 % level of significance is assessed and a p value of <0.05 is considered statistically significant.

5. Results

There were no significant differences in complications between the two groups (Table 1). There were no significant intergroup differences in the total score and score for three upper gastrointestinal symptoms before the start of treatment according to the Izumo scale. There was significant difference for each symptom score after the drug treatment between the two groups. More significant difference was observed in group 1 in comparison with group 2 after drug treatment (Table 2). GERD, FD and total score were significantly higher in group 2 compared with group 1 according to F-scale score. The reductions from baseline in the total score and GERD score differ significantly between the two treatment groups after the drug treatment. The reductions from baseline in the FD score did not differ significantly between the two treatment groups (Table 3). The proportion of patients with $\geq 50\%$ reduction (responders) in the total score for three upper gastrointestinal symptoms (heart burn, epigastralgia, and epigastric fullness) in the izumo scale was 96.7% in the group 1 and 33.3% in the group2(Table 4). In this patient population, the total score and GERD score were significantly reduced in group 1. FD score were not significant for both groups having GERD score > FD score. In the patient population (n=12), the total score and GERD score were significantly reduced by group 1 for patients having GERD score < FD score (Table 5). In group 2, 1

patient showed GERD score = FD score during the first visit (Baseline score). There was reduction in the value of both GERD and FD score after the completion of the treatment (Table 5). There was significant difference between the two groups

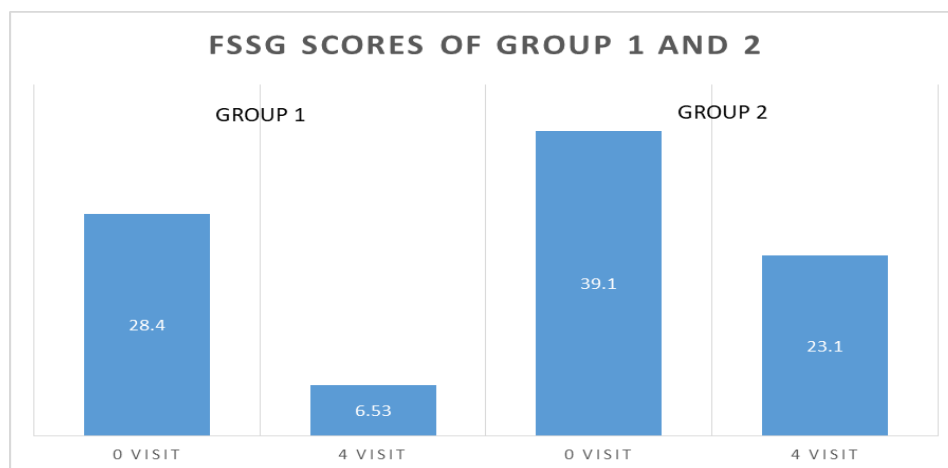


Figure 3:

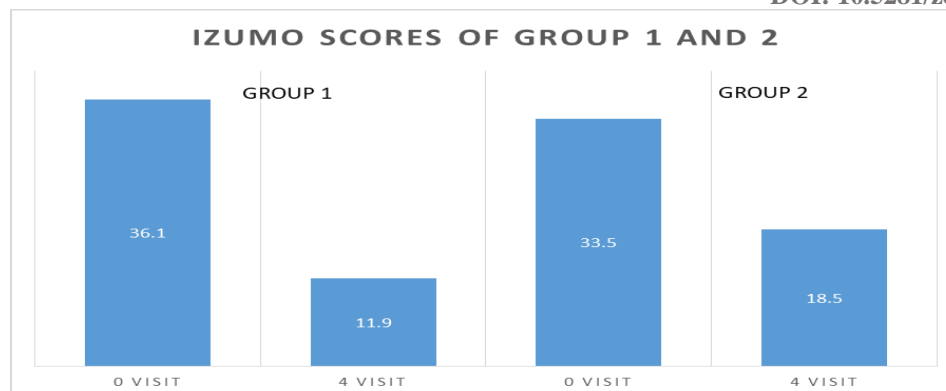


Figure 4:

1) Patients Demographic and clinical characteristics [8]

Demographic Parameters	Total No. of patients	Group 1	Group 2	Total	P-value
		30	30	60	
Gender	Male, n (%)	9 (30.0)	8 (26.7)	17 (28.3)	1.000
	Female, n (%)	21 (70.0)	22 (73.3)	43 (71.7)	
Age (in years)	Mean (SD)	39.3 (12.7)	39.3 (11.5)	39.3 (12.0)	1.000
Height (in cm)	Mean (SD)	161.6 (8.5)	165.9 (8.9)	163.7 (8.9)	0.060
Body Weight (in kg)	Mean (SD)	61.7 (6.5)	65.9 (11.8)	63.8 (9.7)	0.219
BMI (kg/m ²)	Mean (SD)	23.7 (2.3)	23.9 (3.6)	23.8 (3.0)	0.853
Los Angeles Classification n (%)	Group 1	Group 2	Total	P-value	
	30	30	60		
M	14 (46.7)	12 (40.0)	26 (43.3)	0.887	
A	6 (20.0)	8 (26.7)	14 (23.3)		
B	5 (16.7)	6 (20.0)	11 (18.3)		
C	5 (16.7)	4 (13.3)	9 (15.0)		
D	0 (0.00)	0 (0.00)	0 (0.00)		
Complications other than gastrointestinal disorders	Group 1	Group 2	Total	P-value	
	30	30	60		
Ischemic Heart Disease, n (%)	Negative	29 (96.7)	28 (93.3)	57 (95.0)	1.000
	Positive	1 (3.3)	2 (6.7)	3 (5.0)	
Lipid metabolism Abnormalities (%)	Negative	27 (90.0)	26 (86.7)	53 (88.3)	1.000
	Positive	3 (10.0)	4 (13.3)	7 (11.7)	
Thyroid, n (%)	Negative	25 (83.3)	24 (80.0)	49 (81.7)	1.000
	Positive	5 (16.7)	6 (20.0)	11 (18.3)	
Diabetes Mellitus, n (%)	Negative	24 (80.0)	6 (20.0)	49 (81.7)	1.000
	Positive	6 (20.0)	5 (16.7)	11 (18.3)	
Hypertension n (%)	Negative	25 (83.3)	24 (80.0)	49 (81.7)	1.000
	Positive	5 (16.7)	6 (20.0)	11 (18.3)	
Liver Gallbladder and Pancreatic Disorders, n (%)	Negative	30 (100.0)	30 (100.0)	60 (100.0)	NA
	Positive	0 (0.00)	0 (0.00)	0 (0.00)	

The gender distribution of the sample population indicates more females i.e. 43 and males 17 which accounts to a percentage of 71.1% females and 28.3% males. Age distribution of the data indicates that the highest number of patients were in the age group 30-40yrs and the mean age was 39.3. Patients characteristics such as their diet, life style, social habits, occupation, past medical and medication history, personal history were taken into account and depicted in Table 1.

2) Analysis of izumo scale before and after the drug treatment

Intergroup comparisons (Wilcoxon rank sum test)

Izumo scale		Total No. of patients	Group 1 30	Group 2 30	P-value
Before start of the treatment	Total	Mean (SD)	36.1 (6.8)	33.5 (8.5)	0.198
	Three upper gastrointestinal symptoms (heart burn, epigastralgia, and epigastric fullness)	Mean (SD)	12.0 (2.3)	11.2 (2.8)	0.205
	Heart burn	Mean (SD)	11.7 (2.7)	11.5 (3.0)	0.821
	Epigastralgia	Mean (SD)	11.8 (3.0)	10.4 (3.6)	0.121
	Epigastric fullness	Mean (SD)	12.7 (2.6)	11.6 (3.0)	0.135
After start of the treatment	Total	Mean (SD)	-24.2 (6.8)	-15.2 (8.5)	<0.0001
	Three upper gastrointestinal symptoms (heart burn, epigastralgia, and epigastric fullness)	Mean (SD)	-8.1 (2.3)	-5.1 (2.8)	0.0001
	Heart burn	Mean (SD)	-8.1 (2.5)	-5.5 (3.2)	0.003
	Epigastralgia	Mean (SD)	-7.5 (3.4)	-4.5 (3.4)	0.001
	Epigastric fullness	Mean (SD)	-8.7 (2.5)	-5.3 (3.1)	0.0001

3) Changes in F-scale symptom scores (total score, FD score, and GERD score) before and after treatment

Intergroup comparisons (Wilcoxon rank sum test)

F-scale		Total No. of patients	Group 1 30	Group 2 30	P-value
Before start of the treatment	Total score	Mean (SD)	28.4 (10.7)	39.1 (3.1)	<0.0001
	GERD score	Mean (SD)	15.4 (7.2)	22.8 (2.6)	<0.0001
	FD score	Mean (SD)	13.0 (4.9)	16.3 (2.5)	<0.0001
After start of the treatment	Total score	Mean (SD)	-21.8 (10.3)	-16.0 (2.8)	0.011
	GERD score	Mean (SD)	-12.3 (6.7)	-9.3 (2.0)	0.022
	FD score	Mean (SD)	-9.5 (5.1)	-6.8 (1.9)	0.057

4) Proportions of patients with $\geq 50\%$ reduction (responders) in the total score for three upper gastrointestinal symptoms (heart burn, epigastralgia, and epigastric fullness) in the izumo scale: intergroup comparison-Fisher's exact test [8]

izumo scale	Total No. of patients	Group 1 30	Group 2 30	Total 60	P-value
$\geq 50\%$ reduction rate	Patients, n (%)	29 (96.7)	10 (33.3)	39 (65.0)	<0.0001
< 50% reduction rate	Patients, n (%)	1 (3.3)	20 (66.7)	35.0)	

5) Analysis of efficacy by the F-scale score before the start of the study and after completion of the study treatment [8]

F-scale			Group 1 18				Group 2 29				Intergroup difference
Total No. of patients			Visit 1	Visit 4	Change	P-value	Visit 1	Visit 4	Change	P-value	P-value
Patients with GERD score > FD score	Total score	Mean (SD)	32.3 (9.5)	7.6 (3.6)	-24.7 (9.4)	<0.0001	39.2 (3.2)	23.1 (3.8)	-16.1 (2.9)	<0.0001	0.001
	GERD score	Mean (SD)	19.4 (5.2)	3.8 (2.5)	-15.6(5.5)	<0.0001	23.0 (2.5)	13.6 (2.3)	-9.4 (1.9)	<0.0001	<0.0001
	FD score	Mean (SD)	12.9 (4.9)	3.8 (1.7)	-9.1 (4.8)	<0.0001	16.2 (2.5)	9.5 (2.2)	-6.7 (1.9)	<0.0001	0.130
Total No. of patients			12				0				P-value
Patients with GERD score < FD score	Total score	Mean (SD)	22.5 (10.1)	5.1 (2.0)	-17.4 (10.3)	<0.0001	NA				NA
	GERD score	Mean (SD)	9.3 (5.3)	2.1 (1.3)	-7.3 (5.0)	0.004	NA				NA
	FD score	Mean (SD)	13.2 (5.1)	3.0 (1.5)	-10.2 (5.8)	<0.0001	NA				NA
Total No. of patients			0				1				P-value
patients having GERD score = FD score	Total score	Mean (SD)	NA				19.0 (NA)	13.0 (NA)	-6.0 (NA)	NA	NA
	GERD score	Mean (SD)	NA				19.0 (NA)	10.0 (NA)	-9.0 (NA)	NA	NA
	FD score	Mean (SD)	NA				38.0 (NA)	23.0 (NA)	-15.0 (NA)	NA	NA

6) Proportions of patients with $\geq 50\%$ reduction in the GERD and FD symptoms using izumo scale and FSSG scale in different age groups: intergroup comparison

Age (in years)	izumo scale	No. of patients	$\geq 50\%$ reduction rate	< 50% reduction rate		
20 to 39	Group 1	14	14	0		
	Group 2	15	4	11		
40 to 59	Group 1	14	13	1		
	Group 2	13	6	7		
60 to 80	Group 1	2	2	0		
	Group 2	2	0	2		
Age (in years)	FSSG scale	No. of patients	$\geq 50\%$ reduction rate	< 50% reduction rate		= 50 % reduction rate
20 to 39	Group 1	14	12	2		0
	Group 2	15	3	11	1	

40 to 59	Group 1	14	14	0	0
	Group 2	13	1	12	0
60 to 80	Group 1	2	0	2	0
	Group 2	2	0	2	0

More than 50% reduction of symptoms score was noticed in groups belonging to the age group of 20-39 yrs as per the Izumo scale assessment .As per the FSSG scale, >50% reduction of symptoms was seen in patients belonging to the age group of 20-59yrs (Table 6).

Adverse Events: About 10 patients experienced adverse events during treatment comprising 4 patients in the combination group (Group 1) and six patients in the PPI double dose group (Group 2). In the combination group nausea, stomach ache and dizziness were observed. In the PPI double dose group headache, sour taste, loss of appetite, belching was observed. No serious adverse effects were reported. 10 patients were excluded from the study due to H.pylori infection and thus did not comply with the inclusion criteria. This study has its own set of limitations, such as - small patient population, short duration of treatment and lack of placebo control. Finally, this study concludes that the combination group (Acotiamide + Rabeprazole) is more effective than double dose of Rabeprazole in reducing the overlapping symptoms of PPI refractory GERD and FD. It also states that long term therapy with Acotiamide improves patients health related Quality of life.

6. Discussion

This study aims to conduct a comparative evaluation of effectiveness of Acotiamide with Rabeprazole vs. double dose Rabeprazole for symptomatic relief in patients with PPI refractory GERD having overlapping symptoms of Functional dyspepsia (FD). This study was conducted for a period of 6 months with three follow ups. The duration between each follow up was one month. Sixty patients were enrolled in the study after confirming the presence of PPI refractory GERD and FD endoscopically. Patients were randomized in two groups. Group 1 was administered a combination of Acotiamide (200mg/day) and Rabeprazole (20mg/day) and group 2 was given a double dose of Rabeprazole(40mg/day). The severity and frequency of symptoms in each follow up was assessed using standard Izumo and FSSG scale questionnaires. Significant psychological stress was noted in patients, which contributes to Functional dyspepsia. This is the first such study conducted in Indian population. Earlier this study was conducted in Japan in the year 2017 and concluded that no significant difference was found between the effectiveness of both groups (Acotiamide +PPI vs. Double dose PPI).It also added that the use of PPI for long term can lead to Adverse effects like dementia, venous thromboembolism and immunosupresion. Thus, Acotiamide can be an option for long term use. However, the results vary with Indian population due to difference in diet, lifestyle and genetic composition of patients. A core symposia held in Japan from 2015-2017 entitled as “New medical approach to Functional dyspepsia” stated Acotiamide as a newly listed treatment option for Functional dyspepsia.[12]Another study conducted in Japan in the year 2017 concluded that recurrence of dyspeptic symptoms is common and thus adhering to treatment is necessary, it added that Acotiamide is a safe drug for long term use.[13] Following its approval in India a multicentric study was conducted by Lupin Pharmaceuticals in 2018 where data collected from 148 gastroenterologists all over India concluded that symptomatic relief with Acotiamide was seen to be obtained as early as 1-2 weeks of therapy with 50% reduction in symptoms. In the present study patients above 18 years of age

were included. Pediatric, pregnant and lactating women were excluded as studies on safety of acotiamide in said population is ongoing. The studies on safety of Acotiamide in pediatric population is expected to be completed by March 2029 according to Pediatric investigation plan of European Medicines Agency.[15]

7. Conclusion

The efficacy of Acotiamide (200mg/day) +Rabeprazole(20mg/day) and PPI double dose(40mg/day) was compared in the present study for patients experiencing heartburn and epigastric fullness symptoms despite taking a standard dose PPI>8 weeks. The study clearly suggests beneficial effects of add-on therapy with Acotiamide to a proton pump inhibitor for treatment of symptoms in patients with PPI-refractory GERD and FD. Considering the long term treatment required, the combination therapy is an effective option for persistent symptoms in these patients.

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