A PROSPECTIVE STUDY ON THE MANAGEMENT OF FUNCTIONAL DYSPEPSIA

Dissertation Submitted to
The Tamil Nadu Dr. M.G.R. Medical university,
Chennai-600032
in partial fulfilment for the requirement of the Degree of

MASTER OF PHARMACY
In
PHARMACY PRACTICE

OCTOBER 2018

DEPARTMENT OF PHARMACY PRACTICE
KMCH COLLEGE OF PHARMACY
KOVAI ESTATE, KALAPATTI ROAD,
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Submitted by
Reg. No.261640605

Under the guidance of
Dr.(Mrs) SUCHANDRA SEN,PROFESSOR

DEPARTMENT OF PHARMACY PRACTICE
KMCH COLLEGE OF PHARMACY
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CERTIFICATE

This is to certify that the research work entitled **"A PROSPECTIVE STUDY ON THE MANAGEMENT OF FUNCTIONAL DYSPEPSIA"** submitted by **Reg. No.261640605** is a bonafide work carried out by the candidate at Gastroenterology Department, Kovai Medical Center and Hospital, Coimbatore, under the guidance of Dr.(**Mrs) SUCHANDRA SEN,** Professor, Department of pharmacy practice and submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment for the Degree of **MASTER OF PHARMACY** during the academic year 2017-2018.

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CERTIFICATE

This is to certify that the dissertation work entitled **"A PROSPECTIVE STUDY ON THE MANAGEMENT OF FUNCTIONAL DYSPEPSIA"** submitted by **Reg.No 261640605** is a bonafide work carried out by the candidate under my direct supervision and guidance at KMCH ,Department of Pharmacy Practice, Coimbatore and submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment for the Degree of **MASTER OF PHARMACY** during the academic year 2017-2018.

DATE: **Signature of the Guide**

PLACE: Coimbatore

DECLARATION CERTIFICATE

I do hereby declare that the dissertation work entitled **"A PROSPECTIVE STUDY ON THE MANGEMENT OF FUNCTIONAL DYSPEPSIA"** was carried out at Gastroenterology Department, Kovai Medical Center and Hospital, Coimbatore and submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment for the Degree of **MASTER OF PHARMACY,** was done under direct supervision and guidance of **Dr.(Mrs).SUCHANDRA SEN.,** during the academic year 2017-2018.

Date :

Place: Coimbatore

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EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"A PROSPECTIVE STUDY ON THE MANGEMENT OF FUNCTIONAL DYSPEPSIA** submitted by **Reg. No: 261640605,** to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment for the Degree of **MASTER OF PHARMACY** in **PHARMACY PRACTICE** is a bonafide work carried out by the candidate at the Department of Pharmacy Practice, KMCH College of Pharmacy, Coimbatore, Tamil Nadu and was evaluated by us during the university examination held on October 2018.

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Date:

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INDEX

ABBREVIATIONS

FD	-	Functional Dyspepsia
PDS	-	Postprandial Distress Syndrome
EPS	-	Epigastric Pain Syndrome
GERD	-	Gastro Esophageal Reflux Disorder
CCK	-	Cholecystokinin
GDNF	-	Glial cell line –Derived Neurotrophic Factor
NGF	-	Nerve Growth Factor
H.pylori	-	Helicobacter pylori
PPI	-	Proton Pump Inhibitor
GI	-	Gastro Intestinal
GABA	-	Gamma Amino Butyric Acid
SF-NDI	-	Short Form Nepean Dyspepsia Index
VAS	-	Visual Analogue Scale
UD	-	Uninvestigated Dyspepsia
IBS	-	Irritable Bowel Syndrome
OTE	-	Overall Treatment Efficacy
LDQ	-	Leeds Dyspepsia Questionnaire
QOL	-	Quality of Life
ACTH	-	Adrenocorticotrophic Hormone

ABSTRACT

BACKGROUND: Functional dyspepsia (FD) is defined by as the presence of symptoms thought to originate from the gastroduodenal region. According to Rome III criteria the main symptoms of functional dyspepsia include postprandial fullness, early satiation, epigastralgia and epigastric burning .In spite of several therapeutic options for the treatment of FD, It can be still confusing to healthcare providers because there is no definite treatment for functional dyspepsia. It is necessary to identify the better therapeutic options for functional dyspepsia. This study assessed the therapeutic outcome and quality of life of patients with functional dyspepsia by treating with proton pump inhibitor, domperidone and acotiamide, and also the efficacy of acotiamide against the other therapeutic options .

METHOD: It was a prospective study conducted on KMCH Hospital,Coimbatore in which a total 60 patients, were divided into three groups. Patients were divided into three groups.(GroupI-Acotiamide+PPI,Group II-Domperidone+PPI,Group III-PPI). Patients details were collected from data collection form and symptom analysis carried out using Visual Analogue Scale.Quality of life of patients was assessed by using Nepean Dyspepsia Index(SF-NDI) questionnaire. The paired student 't' test was conducted to analyze the difference in score after each group of treatment and also to assess the efficacy of acotiamide were studies using SPSSv20.0.

RESULTS: By this study it was found that the overall symptom score was reduced in acotiamide and domperidone therapy.($p<0.001$ and $p= 0.042$).While in PPI the overall symptom was not significantly reduced. Overall SF-NDI score showed a significant greater improvement from baseline ($p=0.000$), Similarly all the five SF-NDI subscale scores showed improvement than other two groups. There is significant improvement in the abdominal bloating, postprandial fullness, abdominal pain, excessive belching, heart burn, upper abdominal discomfort.

CONCLUSION: Cases with functional dyspepsia have characteristics of middle age,male predominance, Non vegetarian food consumers are more prone to develop FD. From this study it was concluded that acotiamide has better efficacy than PPI monotherapy ,and combination of PPI and domperidone therapy.

1. INTRODUCTION

Dyspepsia is a term derived from a Greek word "dys" (bad), "pepsis"(Digestion) which means bad digestion[1]. Functional dyspepsia is a disorder thought to originate from upper part of gastrointestinal tract. It occurs in general population and is a highly prevalent condition with major socioeconomic and health care impact[2]. There are two types of dyspepsia. Investigated and uninvestigated dyspepsia. Investigated dyspepsia or organic dyspepsia is with organic or metabolic cause and involves peptic ulcer disease, Gastroesophageal reflux disease (GERD) with or without esophagitis, malignancy, pancreaticobiliary disease, uses of certain types of drug and H. *pylori* gastritis. Uninvestigated dyspepsia or functional dyspepsia develops in the absence of systemic, organic and metabolic disease.[3]

COMMON SIGN AND SYMPTOMS [4, 5]

- Postprandial fullness
- Early satiation
- Epigastric pain
- Abdominal bloating
- Abdominal belching
- Nausea
- Vomiting
- Heart burn.

RISK FACTORS

Various risk factors have been found to have associated with dyspepsia, they are.

- Helicobacter *pylori* (H-*pylori*) infection.
- Psychiatric disorders
- Behavioral changes[4]

The Rome III criteria distinguishes functional dyspepsia from other structural disorders. Based on Rome III consensus, FD is subdivided into two categories postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS), characterised by postprandial fullness and early satiation. It is also referred as meal related FD. Epigastric pain syndrome shows symptoms of epigastric pain and burning sensation.[6]

Approximately 20-30% patients are affected with FD in general population. The pathophysiology of functional dyspepsia is unknown, because of its heterogeneous nature. Different management approaches are needed for different patients with distinct underlying pathophysiologies. Genetic factors is one of the reason for individuals to develop functional gastro intestinal disorders, environment factors and patient attitude and behavior also play a important role in developing functional disorder, psychological disorders like patients stress also leads to functional dyspepsia.[1,4]

Table 1

	Pathophysiologically relevant factors
Motility disorder	• Unbalanced volume distribution in the stomach. • Low volume uptake in drinking test • Antral hypomotility and reduced antral migratory motor complexes. • Uncoordinated antroduodenal motility • Increased postprandial duodenal motility. • Impaired volume accommodation of the fundus
Sensorimotor disorders	• Reduced excitability of enteric nerves in the duodenum. • Decrease in Parasympathetic tonus • Increase in Acid sensitivity in the duodenum • Increased Fat sensitivity in the duodenum associated with improved CCK sensitivity.

Visceral hypersensitivity	• Increased Sensitivity after stomach expansion (on an empty stomach and after a meal) • Increased Sensitivity after duodenal, jejunal, and rectal expansion
Immune activation	• Increased GDNF, eosinophilic granulocytes and macrophages in duodenal mucosal biopsy samples • Increased degranulation of the eosinophilic granulocytes in the duodenum • TH2-mediated response in the duodenum • Increased GDNF and NGF expression in the *H. pylori*-positive gastric mucosa
Dysfunctional intestinal barrier	• Increased Permeability in the proximal small intestine
Genetic predisposition	• Increase in GNβ3-TT genotype (increased signal transduction between receptor and target protein) • Decrease in CCK-A receptor CC genotype
Biopsychosocial factors	• Anxiety, depression. Increased Experience of abuse, stressful life events • Decrease in Functional connectivity of brain regions
Altered microbiota	• Increase *Prevotella* • *Helicobacter pylori*

Pathophysiology of functional dyspepsia[1]

DIGNOSTIC INVESTIGATIONS OF DYSPEPSIA

Patients with dyspepsia who undergo upper GI investigation and have pathological finding may be responsible for the symptoms, such as peptic ulcer, are categorized as having organic dyspepsia [5]. Upper GI endoscopy is essential to investigate the FD patients and there by to excluding other structural diseases, before diagnosis of FD upper endoscopy with biopsies and laboratory tests were performed in order to exclude the infections, peptic ulceration, celiac disease and neoplasia[7].

Uncontrolled functional dyspepsia affects very weakly the quality of life of patients and social expenses.[5] The quality of life (QOL) in FD patients is known to be impaired due to symptoms causing emotional distress, problems with food and drink, and impaired vitality[8].

TREATMENT

The treatment of FD is confusing to health care providers, currently there is no definite treatment for FD. Wide range of therapies are available for the management of functional dyspepsia. *H pylori* is the main cause of peptic ulcer disease but its role in non-ulcer dyspepsia is not well known. It is important that physicians be able to recognize dyspepsia, investigations and diagnostic tests and recommend effective treatment in order to avoid possible adverse drug reactions and to improve the quality of life of patients.[9, 10]

- Acid suppressive drugs
- Helicobacter *pylori* eradication treatment
- Antidepressant
- Psycotherapy.
- Prokinetics

Acid Suppressive Drugs

In patients major symptoms of gastrointestinal disorders, acid suppressive therapy is mainly used. Proton Pump inhibitors showing 10-15 % improving symptoms for FD patients.[6]

Proton Pump Inhibitors (PPIs)

Patients with FD, mainly those with epigastric pain syndrome proton pump inhibitors (PPIs) or histamine type 2-receptor antagonists (H_2 blockers) seems to be suppress the gastric acid secretion and relieves the epigastric pain or burning. The initial gastric acid emptying play a pathogenetic role on symptom generation through early onset of duodenal brake, so acid suppression might be successful. Proton pump inhibitor (PPI) are the strongest drug for gastric acid suppression .PPI will block gastric acid secretion by blocking H^+ ion secretion from the parietal cells. They have few adverse effect and are well tolerated by for long term- use. Inhibitors of acid secretion are therefore prescribed for world wide. Although treatment with acid suppression produces symptom relief in a proportion of patients with FD. Retention of PPIs in the stomach for longer time may results in an impaired suppression. Omeprazole is a highly effective PPI which inhibit gastric acid secretion by blocking H^+/K+-adenosine triphosphatase in parietal cells.[11-13]

H. *pylori* Eradication Therapy

Helicobacter pylori infection is the main cause of gastritis, gastroduodenal ulcers and other gastrointestinal disorders. The first line of treatment for *H pylori* eradication consists of proton pump inhibitor (PPI) or ranitidine bismuth citrate, with any two antibiotics among amoxicilline, clarithromycin and metronidazole given for 7-14 days. H. *pylori* is the most common cause of chronic bacterial infection in humans. 20 to 90%, of population include this infection depending on conditions of development and hygiene. The prevalence of H. *pylori* infection in patients with FD varies from 30 to 70%. It is known that H. *pylori* can cause dyspeptic symptoms, inducing motor disorders, causing visceral hypersensitivity, acid secretion alterations, active and persistent inflammation.[14,15]

Antideppressant

Tricyclic antidepressants showed beneficial effect from the symptoms of FD. The mechanism of action of antidepressants is not clearly understood for

gastrointestinal disorders, although there is some evidence that the drugs affect gastric sensitivity. Serotonin/noradrenalin reuptake inhibitor such as venlafaxine failed to show any beneficial effect in FD. While Paroxetine, a selective serotonin reuptake inhibitor (SSRI), enhanced gastric accommodation .[16]

Psychotherapy

Interpersonal psychotherapy may be effective in FD patients. The prevalence of psychiatric symptom is high among FD patients. So improvement of these symptoms following psychotherapy in functional gastrointestinal disorders appears to be related with reduced psychological distress and improved health condition.[17]

Prokinetics

Prokinetics are the medications used for enhancing gastric motility acting through receptor. It acts by increasing esophageal sphincter pressure, enhancing esophageal peristalsis, gastric emptying and bowel movement [16].

Domperidone

Domperidone, is peripheral dopamine D_2 antagonist ,blocking dopamine in the enteric nervous system, It acts centrally in the chemoreceptor trigger zone, thus by reducing the nausea and ,It also effects motor function and thus improves the gastric emptying and peristaltic movement of intestine. So domperidone acts as an antiemetic and prokinetic agent. Domperidone had a good safety profile and is treated for FD. It is also used as a therapeutic option for variety of GI motility disorders such as gastroparesis and gastrooesophagal reflux disorder. But domperidone shown several adverse effect such as increase plasma prolactin level on long term treatment .It does not cross the blood –brain barrier and a lower cardiovascular risk while having good clinical efficacy.

Omeprazole and domperidone given in combination did not have any clinically relevant pharmacokinetic interactions. Combination therapy of PPI and

prokinetics increases symptomatic relief from FD than PPI monotherapy. It may improve patient quality of life.[18,12]

Acotiamide

Acotiamide is a novel prokinetic agent, it has various pharmacological effects on the gastrointestinal tract. which inhibits acetyl choline esterase and exerts its gastroprokinetic activity by enhancement of acetylcholine release. Acotiamide is a muscarinic receptor antagonist in the enteric nervous system. It blocks M_1 and M_2 receptor that alter acetylcholine release. Acotiamide was shown to improve dyspepsia symptoms by increasing both gastric accommodation and delayed gastric emptying. It relieves both symptoms of epigastric pain syndrome and postprandial distress syndrome. Acotiamide also inhibit stress related hormones. Acotiamide modulates upper gastrointestinal movement to improve abdominal symptoms resulting from hypomotility. [19, 20]

This drug was first launched in Japan in June 2013 as a therapeutic agent for FD. A phase III trial was done in Europe, and a phase II trial was finished in USA. Acotiamide have ability to alter the expression of stress related genes such as GABA and neuromedin U in medulla oblongata or hypothalamus. So there by acotiamide has an important role in the regulation of stress through the hypothalamic-pituitary-adrenocortical activity. The dose of acotiamide 100mg three times a day shown a overall improvement in the symptoms without any significant adverse events.[21]

Prokinetic therapy has been found to have a positive effect on functional dyspepsia but is still not conclusive. The present study will also assess the efficacy of acotiamide against the other therapeutic options for FD.

This study will assess the therapeutic outcome and quality of life of patients with functional dyspepsia who are on any one of the following treatment options --- proton pump inhibitor, domperidone and the prokinetic agent acotiamide, and thereby compare the three to predict efficacy.

2. REVIEW OF LITERATURE

- **Ibnu Fajariyadi Hantoro *et al* (2018)**; Conducted a study to determine the contribution of clinical, psychosocial, and demographic factors in affected functional dyspepsia patients in Indonesia. 124 patients were enrolled in the study, HRQoL was measured using the Medical Outcomes Study Short-Form 36 (SF-36) physical component summary (PCS) and mental component summary (MCS) . The factors investigated were age, gender, symptom severity, education level, employment status, anxiety, depression, and ethnicity. The Results supported that all domains of HRQoL except vitality were impaired in patients with functional dyspepsia. From this study it was concluded that there was significant HRQoL impairment in patients with functional dyspepsia in Indonesia.[22]

- **Varsha Narayanan *et al* (2018)**; carried out a study on 314 FD patients with meal-related-symptoms, received acotiamide 100 mg thrice daily for 4 weeks. Improvement of the symptoms were evaluated by a questionnaire, as well as tolerance to treatment. The results supported that complete relief or significant improvement from postprandial fullness, upper abdominal bloating and early satiety was achieved. Mild adverse events were reported by 6% patients; mainly headache, nausea, vomiting, vertigo, burning sensation, palpitation, and epigastric pain. From this study it was concluded that acotiamide improved the meal related FD symptoms with good safety profile.[23]

- **Young Li *et al* (2018)**; conducted a study to evaluate sleep quality and mood symptoms in FD, assessing association of FD severity ,disordered sleep, psychological symptoms.115 patients were enrolled in this study .sleep disorder was assessed by Pittsburgh sleep quality index(PSQI),and symptom checklist-90-reviced (SCL-90R) was used to determine depression, anxiety and epigastric pain syndrome. The results suggests that lower educational level ,and sleep disturbance were independently associated with FD. This study found that FD was associated with sleep disorder and psychological therapies may help to reduce FD symptoms[24]

- **Agneta Uusijarvi *et al* (2018);** Performed a study to validate Rome III criteria and alarm symptom and their ability to distinguish between organic and functional dyspepsia. 258 children's aged 4-17 years with gastrointestinal complaints, and who consulted for secondary or tertiary care in Stockholm were enrolled in the study. Data's were collected by using questionnaire on pediatric gastrointestinal symptom Rome III. The results supported that 16% having organic disorders 54% having pain predominant functional gastrointestinal disorder and 30% having other functional diseases .From this study it was concluded that combining the Rome III criteria and absence of alarm symptoms from patient questionnaire had high specificity but low sensitivity.[25]

- **Satoshi schinozaki *et al* (2017)**; Carried out a study based on adherence to an acotiamide improves long term outcomes in patients with functional dyspepsia. 79 patients with functional dyspepsia were enrolled in the study who underwent esophagogastroduodenoscopy. Symptoms and followed for more than one year. Symptom severity assessed by using the lzmo scale and analysed by using Kaplan-Meier method. The study concluded that recurrence of functional dyspepsia for long term is in higher rate. While adherence towards acotiamide decreases the rate of reappearance of dyspeptic symptoms.[26]

- **J. Tack *et al* (2017);** Conducted an open-label safety trial to evaluate the long-term safety and efficacy of acotiamide on PDS symptoms. Patients (defined by ROME III criteria) aged ≥18 years with active PDS symptoms were enrolled to receive 100 mg acotiamide three times daily for 1 year .Patients safety and efficacy of acotiamide was monitored by using the validated LPDS, quality of life using SF-36 and SF-NDI questionnaires, and work productivity using WPAI. The study concluded that acotiamide has the long-term safety in treatment of FD, and also a remarkable change for PDS symptoms, QOL, and work productivity was suggested [8].

- **Rasmirekha Behera *et al* (2017);** Conducted a study to assess the efficacy and Safety of Acotiamide and Levosulpiride in Functional Dyspepsia **.** 60 patients were

selected for the study. Patients were divided into 2 groups. Group A received 100mg acotiamide TDS before meal for 8wks.Group B received levosulpiride 25 mg TDS for 8 wks. Treatment outcome categorized as excellent: Complete relief of symptoms, Good: improvement with only occasional symptoms, nil: no improvement. The result supported that the Patients treated with Acotiamide showed more improvement in symptoms of FD and better tolerated in comparison to Levosulpiride. This study concluded that the Acotiamide found to be quiet safe and effective drug in patients of Functional Dyspepsia in comparison to Levosulpiride.[27]

- **KY Marakhouski *et al* (2017);** Done randomized controlled, phase 4 study, to compare the efficacy and safety of omeprazole-domperidone combination with omeprazole monotherapy in gastroesophageal reflux disease (GERD).60 patients were enrolled in this study they received group 1 (omeprazole20 mg+domperidone 30 mg) or group 2 (omeprazole 20 mg) in an equal ratio; 2 capsules daily in the morning were administered for 8 weeks. Symptom severity was assessed by visual analogue scale (VAS) and GERD-Q questionnaire. The study concluded that Omeprazole-domperidone combination was more effective than omeprazole alone. [12]

- **Basha Ayele *et al* (2017)**; Done a study to determine the contributing factors for dyspepsia at Yirga cheffe primary hospital, southern Ethopia.168 patients were enrolled in the study, face to face interview was taken to assess the contributing factor for the infection. The result supported that helicobacter pylori infection was six times associated with dyspeptic patients than non-Dyspeptic individuals. anxiety and depression was six and three times more likely associated with dyspepsia, dyspepsia was greater among male, and peaked in the age groups of 21-30 years old, patients who consume foods containing peppercorn, who depend on untapped drinking water sources, smoking habit, chewing khat. This study concluded that early diagnosis of H. pylori ,psychological treatment of patients and food habit of the individuals should give attention to prevent and control dyspepsia.[5]

- **Young Joo Yang *et al*** (2017) ; Performed a randamised controlled trials (RCTs) of prokinetics for treatment of FD. In total 25 RCTs 4473 patients were included who were treated with 6 different prokinetics. Symptoms score was analysed by odds ratio. Beysian net work analysis was performed for this study. Study suggests that metoclopromide, trimebutein, mosapride, and domperidone showed better efficacy for FD treatment than acotiamide and or itopride [28]

- **Tareq Al Saadi *et al* (2016)**: Performed a study to estimate the epidemiologic characteristics and possible risk factors for UD, IBS, and GERD among students at Damascus University, Damascus, Syria. 302 valid participants were enrolled in the study. The results supported that prevalence for UD, IBS, and GERD was 25%, 17%, and 16%, respectively. Symptom overlap was present in 46 students (15%), with UD+ IBS in 28 (9.3%), UD + GERD in 26 (8.6%), and IBS + GERD in 14 (4.6%) students. Eleven (3.6%) students had symptoms of UD +IBS+GERD. From this study it was concluded that risk factors for these disorders remain poorly characterized and need further investigations.[29]

- **Hiroyuki Osawa *et al* (2016);** Conducted a study to assess effect of acotiamide in patients with functional dyspepsia.51 patients were enrolled in study who treated with acotiamide and followed them for more than one year. Patients quality of life and symptom severity was assessed by using the Izumo scale.The results supported that acotiamide showed a greater improvement on epigastric syndrome (EPS) and postprandial distress syndrome(PDS).From this study it was concluded that acotiamide treatment improves and resolves EPS symptoms and PDS symptom take more longer to resolve than EPS symptoms.[30]

- **R Bitwayiki *et al* (2015);** Performed a cross sectional survey on prevalence of dyspepsia and impact of quality of life among Rwandan healthcare workers(HCWs). Quality of patients was assessed by using questionnaires, including short of dyspeptic symptoms, and short term Nepean dyspepsia index(SF-NDI). In this study 378 enrolled HCWs all of whom provided response to SF-LDQ and 356 whom responded to SF-NDI. The results showed that tension and eating/drinking

subdomain of the SF-NDI had more effects. This study suggested that the prevalence of dyspepsia among HCWs in Rwanda is a high and associated with lowered quality of life.[31]

- **Hiroshi yamawaki *et al* (2014);** Conducted a study on Twenty-five functional dyspepsia (FD) patients were treated with acotiamide (300mg/day) for 4 weeks. Anxiety was evaluated using STAI-state/-trait. ACTH and cortisol levels measured in FD patients. Acotiamide treatment significantly improved postprandial fullness and early satiety in 4 weeks treatment in FD patients compared to those in pretreatment. Acotiamide did not affect anxiety using STAI-state/-trait as well as ACTH and cortisol levels in FD patients. This study suggested that further studies is needed for more clarification of improvement of FD symptoms in acotiamide therapy.[32]

- **Shuhei mayanagi *et al* (2014);** Done a study to evaluate the efficacy of an initial PPI followed by a combination therapy and PPI and acotiamide.105 patients were enrolled who started an initial PPI. 23 patients with residual symptoms receives 100mg acotiamide three times a day with esomeprazole as a combination therapy for 2 weeks. The symptoms were evaluated using the modified frequency scale (mFSSG) almost all FD related symptoms improved after combination therapy with an improvement in the mFSSG Score. The findings suggest that the combination therapy of acotiamide and PPI may be effective in selected FD patients as compared with an initial PPI therapy.[33]

- **Hiroshi Kaneko *et al* (2014);** Performed a study to providing awareness of functional dyspepsia and Rome criteria among Japanese internist.1623 subjects were internist ,1660 were doctors,4264 attendees were enrolled .self administering questionnaire were used for data collection. The results supported that existence of Rome criteria was known in 39.9% of internist. from this study it was concluded that awareness was needed for the medical medical term FD in Japan and revision of Rome criteria for routine clinical practice.[34]

- **Chatchai Kriengkirakul *et al* (2012)**; Conducted a study to evaluate the efficiency of proton pump inhibitor (PPI) treatment on patients with overlapping non-erosive gastroesophageal reflux disease (NERD) and functional dyspepsia (FD).60 patients were enrolled in the study who were underwent treatment of rabeprazole 20 mg b.i.d. for 2 weeks. The symptoms were evaluated using a symptom questionnaire with 4-point Likert scales before and after treatment. The result supported after the PPI treatment, epigastric burning, acid regurgitation, heartburn, nausea, vomiting and chest discomfort scores were significantly improved compared to pretreatment values, whereas postprandial abdominal fullness, early satiation, belching and food regurgitation were not. From this study it was concluded that the two-week high dose PPI treatment was not effective for early satiation, postprandial abdominal fullness, regurgitation or belching symptoms [35].

- **Ford, AC *et al* (2011)**; conducted a study about the Rome III criteria .For in this study 1452 adult patients with GI symptoms enrolled . Individuals with normal upper GI endoscopy and histopathology findings from analyses of biopsy specimens were classified as having no organic GI disease. This study Concluded that In a validation study of 1452 patients with GI symptoms, the Rome III criteria performed for identifying and diagnosing functional disorders from other gastrointestinal disorder[36].

- **Kei matsueda *et al* (2011);** Conducted a placebo controlled trial in which 450 patients with functional dyspepsia who received 100 mg acotiamide and 442 patients allocated to placebo three times a day for 4 week. Efficacy of treatment was assessed by overall treatment efficacy (OTE) scale and elimination rate of each three meal related symptoms such as Postprandial fullness, Upper abdominal bloating and early satiation were evaluated. The results supported that there is no any cardiovascular adverse events, and a significant improvement in quality of life of FD patients. The study found that acotiamide significantly improved symptom severity and eliminated meal related symptoms in patients with FD. [4]

- K. **Matsueda *et al* (2011)** ; Performed a multicenter, open-label, single-arm, long-term phase III study in which patients with FD were given acotiamide, 100 mg t.i.d, for 48 weeks long-term study of acotiamide. The study was carried out to investigate the efficacy, safety and administration pattern of acotiamide in patients with functional dyspepsia (FD). 405 patents were enrolled in this study and the efficacy was analyzed by OTE improvement rate, the symptom elimination rate increased. This study supported that FD symptoms were controlled by intermittent administration of acotiamide even in patients with relapsing FD.[2]

- **Suzanna Ndraha *et al* (2011);** Carried out a study on 60 dyspeptic patients with heartburn and/or regurgitation were enrolled to evaluate the efficacy of combination of PPI with prokinetic drug compared to PPI mono therapy in GERD patients with high frequency scale for the symptoms of GERD (FSSG) score. They were divided into two groups. Group A was given omeprazole 2x20 mg and domperidone 3x10 mg for 2 weeks, while another group was only given omeprazole 2x20 mg. The FSSG score was performed before treatment and after 2 weeks of treatment. The study reveals that combination of omeprazole with domperidone in GERD patients with high FSSG score is better than compared to omeprazole monotherapy.[13].

- **Yasuhiro Fujiwara *et al* (2011)**; Conducted a study on Japanese workers to identify association of cigarette smoking with functional dyspepsia ,GERD or irritable bowel syndrome.2680 eligible subjects were enrolled in the study. The results suggest that cigarette smoking was a common factor associated with overlaps of FD,GERD or irritable bowel syndrome, The association is stronger in smokers who smoked ≥1 pack per day as compared to those who smoked less than 1 pack per day. This study concluded that cigarette smoking was significantly associated with overlaps of GERD, FD and IBS among Japanese adults [37].

- **Guilherme Becker Sander *et al* (2011)*;*** Done a study to measure the influence of dyspepsia on work productivity of people within the Brazilian workforce.850 adult patients were enrolled in the study. All patients answered a demographic questionnaire. Productivity impairment was measured by the Work Productivity and

Activity Impairment questionnaire. Subjects underwent upper gastrointestinal endoscopy and were classified as having functional or organic dyspepsia. The results supported 387 (45.5%) were active workers and 78% reported a reduction of the work productivity (presenteeism). The affect on work productivity was similar between patients with functional or organic dyspepsia. This study showed an important influence of dyspepsia on work productivity [38].

- **Jauregui Lobera et al (2011)**; conducted a study Impact of functional dyspepsia on Quality of life in eating disordered patients. 78 patients were enrolled in the study the Symptoms of dyspepsia, the related quality of life, anxiety, depression were evaluated. The results supported that early satiation and bloating were significantly higher in FD Patients. The study concluded that FD constitute a general bias common to all eating patients with specific effect on the characteristic symptoms of FD .[39]

- **Sheng-Liang Chenloss *et al* (2010);** conducted a study with Eighty-five consecutive Chinese patients with FD. This study was to investigate the incidence of nocturnal dyspeptic symptoms in patients with functional dyspepsia (FD) and whether prokinetic drugs can alleviate them. Baseline nocturnal intragastric pH, bile reflux and nocturnal dyspeptic symptoms of eligible patients, including epigastric pain or discomfort, abdominal distention and belching, were investigated with questionnaires after one year. The result supported that domperidone can alleviate nocturnal dyspeptic symptoms, which may be interrelated with the excessive nocturnal duodenogastric bile reflux.[18].

- **Sanjiv Mahadeva *et al* (2009);** Conducted a study to validate English and locally translated version of the Short-Form Nepean Dyspepsia Index (SF-NDI) in Malaysian patients who consult for dyspepsia. English and Malay versions of the SF-NDI were assessed against the SF-36 and the Leeds Dyspepsia Questionnaire (LDQ), examining internal consistency, test-retest reliability and construct validity. 143 patients (86 English-speaking and 57 Malay speaking) with dyspepsia were enrolled in the study and interviewed them. The results supported that the median total SF-NDI score for

both languages were 72.5 and 60.0 respectively. In both languages, SF-NDI sub-scales and total score demonstrated lower values in patients with more severe symptoms and in patients with functional vs organic dyspepsia. This study demonstrates that both English and Malay versions of the SF-NDI are reliable and probably valid instruments for measuring HRQoL in Malaysian patients with dyspepsia [40].

- **Anjiang Wang *et al* (2008);** conducted a study to investigate the prevalence and risk factors for overlap of FD and IBS based on Rome III criteria.3014 patients were enrolled in study and they were requested to complete the questionnaires. Results supported that patients with IBS and FD shows higher severity scores than those with FD alone. This study reveals that the common risk factor for clinical overlap of IBS and FD is postprandial fullness.[41]

- **M.Pajala *et al* (2006);** Performed a study on 400 patients with dyspepsia to evaluate assurance of primary care of FD and organic dyspepsia patients and influence of GI symptoms and psychological factors by using a completed questionnaire ,and monitored their symptom for one year . The study concluded that the gastrointestinal symptoms for FD is long lasting and investigations shows that patients have lower mental distress and fear illness, psychological factors are related to symptoms severity changes.[42]

- **Sundeep S Shah *et al* (2001)**; Conducted a study on prevalence, demography and economic implications of dyspepsia in India. 2549 healthy individuals were enrolled in the study .gastrointestinal symptoms, their investigations and treatment, dietary history and history of addiction were noted. The results showed that 30.4% had dyspepsia .33.2 % of patients had dysmotility like dyspepsia which is the most common type of dyspepsia. The frequency of dyspepsia was not related to type of diet or consumption of spices. Dyspepsia were more prevalent in in subjects who abused tobacco or alcohol. This study concluded that dyspepsia occurs in one third of the population in Mumbai. Significant symptom occurs in 12%, 40% of peoples were

undergone treatment and only a small number undergone endoscopy or ultrasonography.[43]

- **A L Blum et al (2000);** conducted a study to evaluate the treatment of functional dyspepsia with acid inhibitors. 792 patients were enrolled in the study. Antacid treatment ranitidine 150 mg, omeprazole 10 mg, or omeprazole 20 mg daily. Individual dyspeptic and other abdominal symptoms were evaluated before and after treatment according to *H pylori* status. The results supported that there was no significant therapeutic gain from active treatment over placebo in *H pylori* negative patients. complete improvement of symptoms and quality of life also occurred most frequently with omeprazole 20 mg and was significant in both *H pylori* positive and *H pylori* negative groups. This study concluded that Omeprazole 20 mg had ability to disappear most of the symptoms in *H pylori* positive patients.[44]

- **N.J Talley *et al* (1998);** Performed a study to evaluate the efficacy of proton pump inhibitor therapy in functional dyspepsia.1262 patients with a functional dyspepsia (persistent or recurrent epigastric pain or discomfort for at least 1 month and a normal upper gastrointestinal endoscopy) were enrolled and subjected to receive omeprazole 20 mg, 10 mg or identical placebo, for 4 weeks. Symptoms were assessed using validated measures. Results supported that complete symptom relief was observed in 38% on omeprazole 20 mg, compared with 36% on omeprazole 10 mg and 28% on placebo(P= 0.002 and 0.02, respectively). There was no significant benefit of omeprazole over placebo. Symptom relief was similar in H. pylori-positive and negative cases. From this study it was concluded that Omeprazole is modestly superior to placebo in functional dyspepsia at standard (20 mg) and low doses (10 mg) but not in patients with dysmotility-like dyspepsia. [45]

Kommentar [u1]:

3. AIM AND OBJECTIVE

AIM

To assess the therapeutic outcome and quality of life of patients with functional dyspepsia by treating with proton pump inhibitors, Domperidone and a novel Prokinetic agent Acotiamide.

OBJECTIVES

- To study the prevalence, aetiological factors and characteristics of the functional dyspepsia.
- To identify the treatment options for functional dyspepsia.
- To measure the outcome of the management.
- To assess the quality of life.
- To check adverse drug reaction, if any.

4. METHODOLOGY

STUDY SITE

This study was performed in the Department of Gastroenterology, Kovai Medical Center and Hospital (KMCH), Coimbatore, Tamil Nadu, India. The proposed protocol for the study was presented and approved by the Hospital Ethical committee.

STUDY TYPE

The study was a Prospective observational study on the management of functional dyspepsia, to be undertaken at the Department of Gastroenterology, Kovai Medical Centre and Hospital (KMCH).

STUDY DURATION

The study period was six month. Feb 2018-July.2018.

STUDY CRITERIA

Inclusion criteria:

Patients with functional dyspepsia without any metabolic or systemic disease were included in the study.

Patients having two or more of the following symptoms were included in the study: upper abdominal pain, upper abdominal discomfort, postprandial fullness, upper, abdominal bloating, early satiation, nausea, vomiting, excessive belching.

Exclusion criteria

- Patients with organic causes of gastroparesis (Eg. Diabetes mellitus) and other serious disease (like alcoholism and drug dependence).
- Pregnant and lactating women**.**
- Predominant ulcer like dyspepsia (pain) and symptoms suggestive of irritable bowel syndrome.
- Patient who had undergone any bowel surgery or malignancy.

SOURCES OF DATA

Data were collected from Patients case reports and treatment details and direct patient interview. Details recorded included patients demographics, social habits, co-morbidities, medical history, treatment details and outcomes will be noted in a structured manner in a data collection form.

STUDY TOOLS

- Data collection form
- Visual Analogue Scale
- Short-form Nepean Dyspepsia Index
- SPSS version 20

STUDY PROCEDURE

Patients were divided into three groups. In one group patients were treated with PPI a combination of PPI and acotiamide, In the second group patients were treated with combination of PPI and domperidone, and in third group patients were treated with PPI alone.

STUDY POPULATION

A total of 70 patients who fulfill the inclusion criteria included in my study, 10 patients were excluded by the reason of non complaints. All the 60 patients were enrolled and divided into three groups. The patients demographic information, symptoms, treatment required for the study were collected using a structured questionnaire and also from different data sources available and were recorded in the patient data sheet. Patients characteristics like age, gender, smoking status and alcohol intake, food habits, past medical history, treatment characteristics were noted.

Visual analogue scale was used to measure the symptom severity, it was a 10-cm scale with 0 (no symptom) to 10 (maximum symptom severity) .Visual analogue scale was used to measure patients response at the time of enrollment and review after 28 days for the symptoms improvement analysis and then compared.

Quality of Life

Nepean dyspepsia index questionnaire is a questionnaire comprising ten item, making up five subscales of two items each that examine the impact of dyspepsia on various domains of quality of life of patients, including tension/anxiety, disruption of regular eating/ drinking. Knowledge and control over disease symptoms and interference with work/study. It was used to assess the quality of life of patients with functional dyspepsia with 10 short term questionnaire during the enrollment and review after 28 days for quality of life analysis then compared.

STATISTICAL ANALYSIS :

Demographic details and disease treatment characteristics were studied as percentages. The difference in the visual analogue scale score between enrollment and review was noted. And the difference of Nepean dyspepsia index questionnaire during enrollment and review was also noted. The paired 't' test was conducted to analyze the differences of both VAS score and quality of life questionnaire score. A p value <0.005 was taken to be significant, and there by compare the overall symptom score and questionnaire score for all the groups, and to evaluate the efficacy of each therapeutic option.

5. TABLES AND GRAPHS

TABLE.1 AGE WISE DISTRIBUTION AMONG THE STUDY POPULATION (n=60)

AGE	NUMBER OF PATIENTS(n=60)	PERCENT (%)
25-34	5	8.3
35-44	9	15.0
45-54	24	40.0
55-64	9	15.0
65-74	8	13.3
75-84	5	8.3
Total	60	100.0

Fig.1 AGE WISE DISTRIBUTION AMONG THE STUDY POPULATION (n=60)

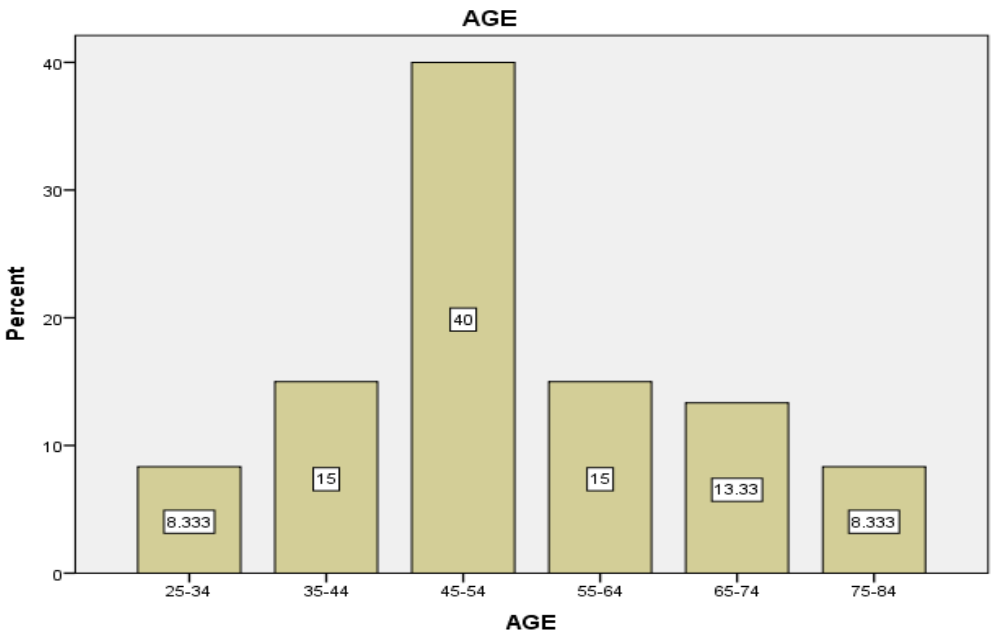

TABLE.2 GENDER WISE DISTRIBUTION AMONG THE STUDY POPULATION (n=60)

GENDER	NUMBER OF PATIENTS(n=60)	PERCENT (%)
Male	38	63.3
Female	22	36.7
Total	60	100.0

Fig.2 GENDER WISE DISTRIBUTION AMONG THE STUDY POPULATION (n=60)

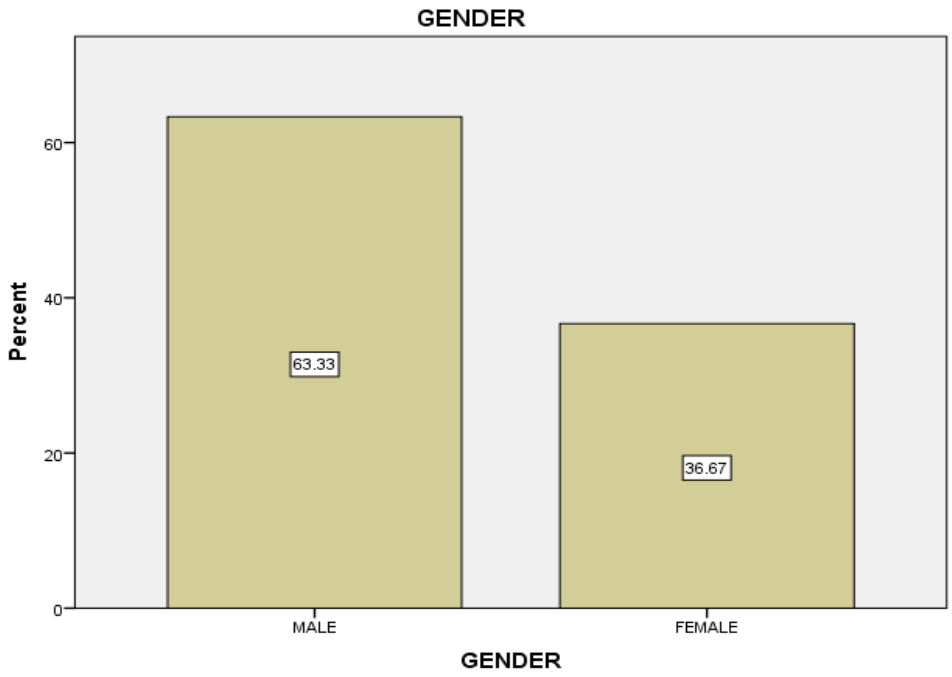

TABLE 3.DISTRIBUTION OF SMOKING STATUS AMONG THE STUDY POPULATION (n=60)

SMOKING	NUMBER OF PATIENTS (n=60)	PERCENT (%)
Past	1	1.7
Never	59	98.3
Total	60	100.0

Fig.3.DISTRIBUTION OF SMOKING STATUS AMONG THE STUDY POPULATION (n=60)

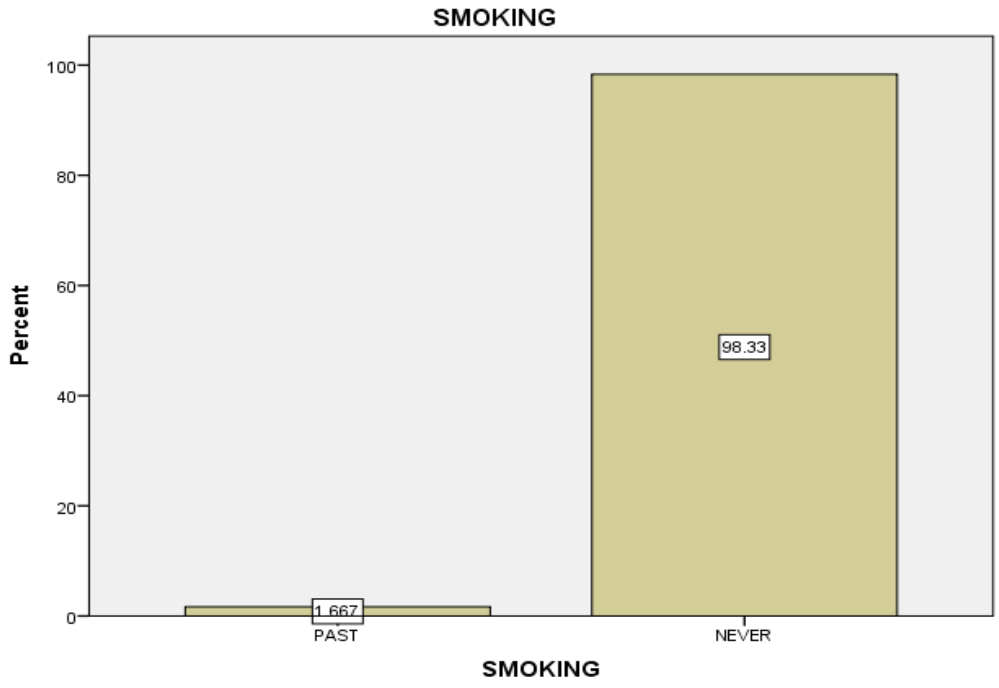

TABLE.4 DISTRIBUTION OF ALCOHOL INTAKE AMONG THE STUDY POPULATION (n=60)

ALCOHOL	NUMBER OF PATIENTS (n=60)	PERCENT (%)
Past	1	1.7
Present	1	1.7
Never	58	96.7
Total	60	100.0

Fig.4 DISTRIBUTION OF ALCOHOL INTAKE AMONG THE STUDY POPULATION (n=60)

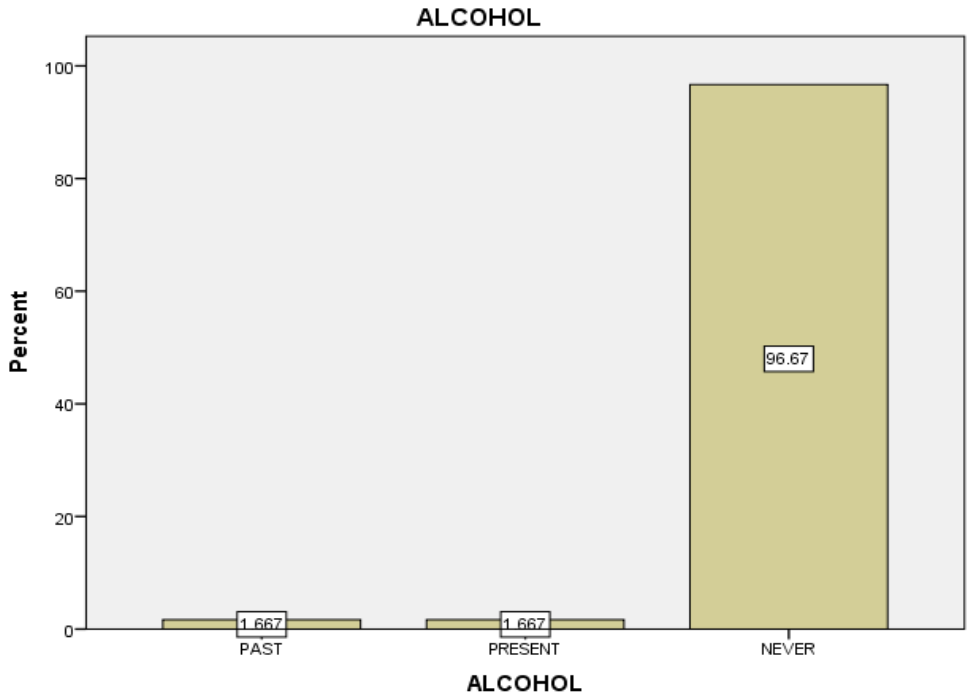

TABLE.5 DISTRIBUTION OF FOOD HABITS AMONG THE STUDY POPULATION (n=60)

FOOD HABIT	NUMBER OF PATIENTS (n=60)	PERCENT (%)
Vegetarians	23	38.3
Non vegetarians	37	61.7
Total	60	100.0

Fig.5.DISTRIBUTION OF FOOD HABITS AMONG THE STUDY POPULATION (n=60)

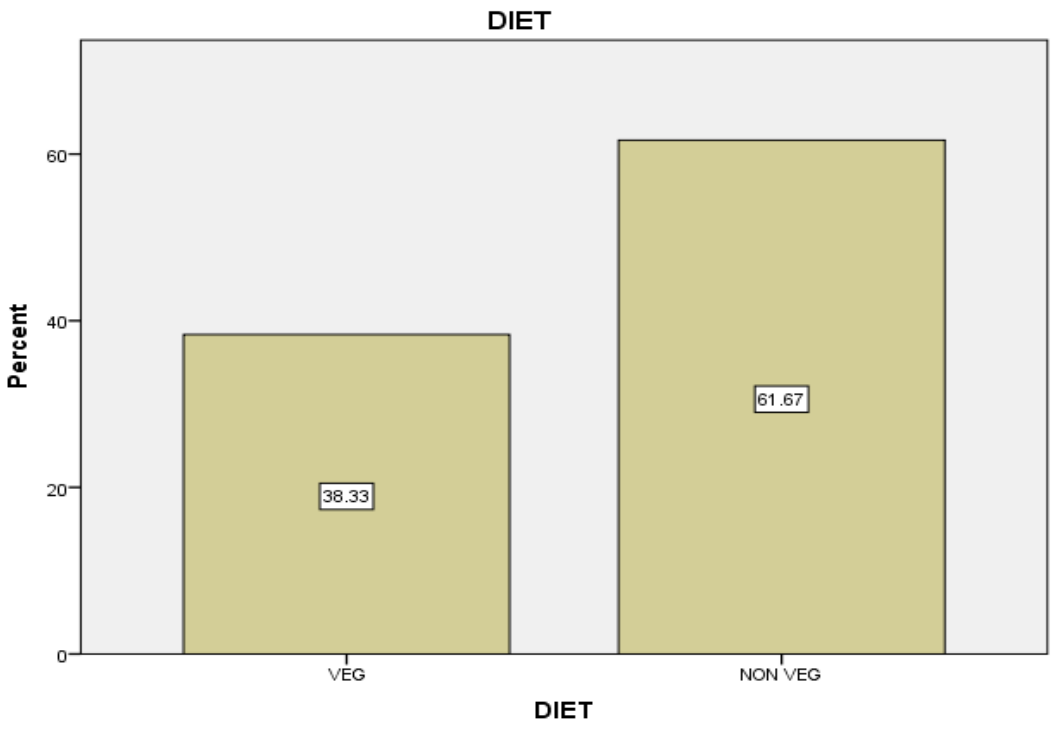

TABLE.6 DISTRIBUTION OF BODY WEIGHT AMONG THE STUDY POPULATION (n=60)

WEIGHT(kg)	NUMBER OF PATIENTS (n=60)	PERCENT (%)
30-60	28	46.7
60-80	30	50.0
80-100	2	3.3
Total	60	100.0

Fig.6 DISTRIBUTION OF BODY WEIGHT AMONG THE STUDY POPULATION (n=60)

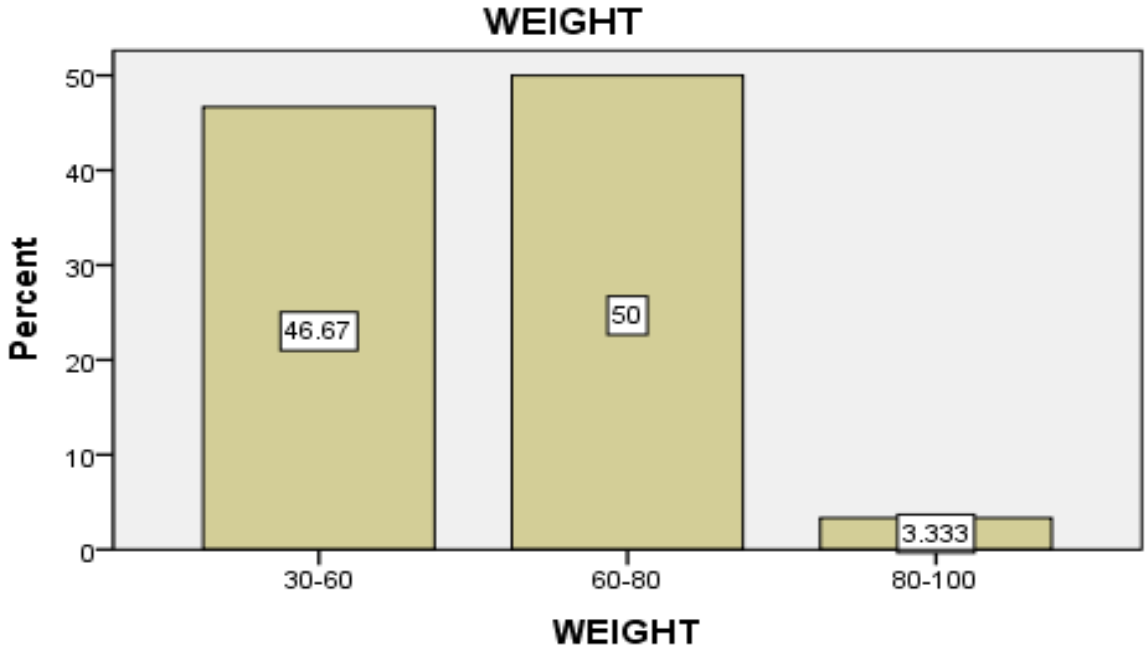

TABLE 7.DISTRIBUTION OF DURATION OF SYMPTOMS AMONG THE STUDY POPULATION (n=60)

DURATION	NUMBER OF PATIENTS (n=60)	PERCENT (%)
1 week	5	8.3
1 month	35	58.3
2 month	10	16.7
6 month	7	11.7
2 month	2	3.3
3 year	1	1.7
Total	60	100.0

Fig.7.DISTRIBUTION OF DURATION OF SYMPTOMS AMONG THE STUDY POPULATION (n=60)

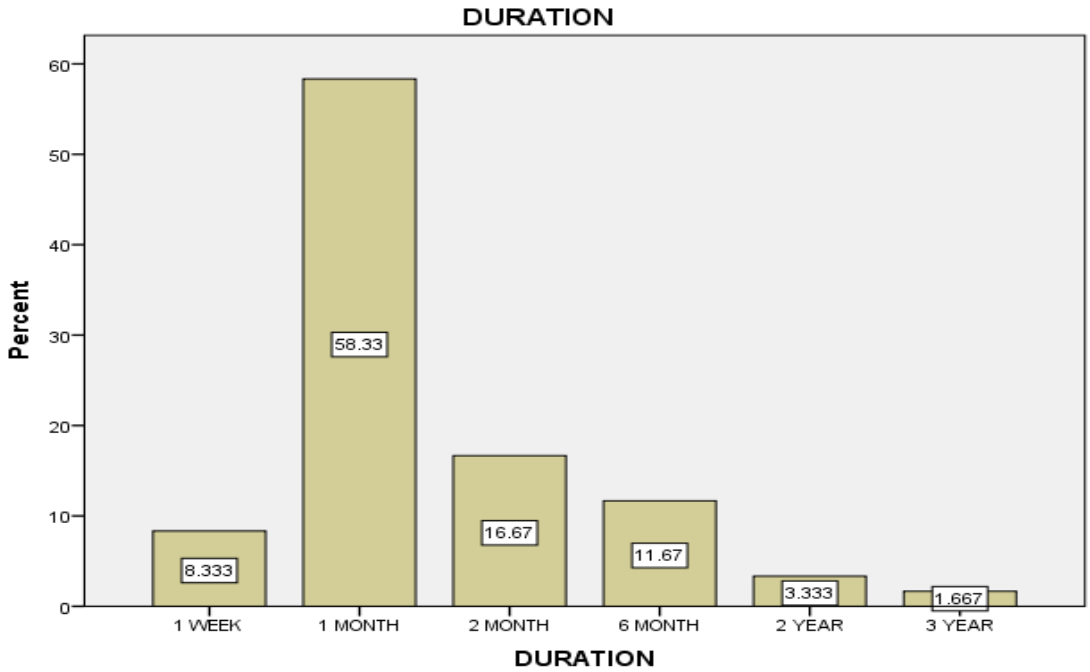

TABLE 8. DISTRIBUTION OF SYMPTOMS AMONG STUDY POPULATION (n=60)

SYMPTOMS	NUMBER OF PATIENTS (n=60)	PERCENT (%)
Postprandial fullness	23	38.3
Abdominal Discomfort	23	38.3
Early Satiation	6	10
Abdominal pain	27	45
Abdominal Bloating	35	58.3
Excessive Belching	12	20
Nausea& Vomiting	14	23.3
Heart burn	22	36.6

Fig.8 DISTRIBUTION OF SYMPTOMS AMONG STUDY POPULATION (n=60)

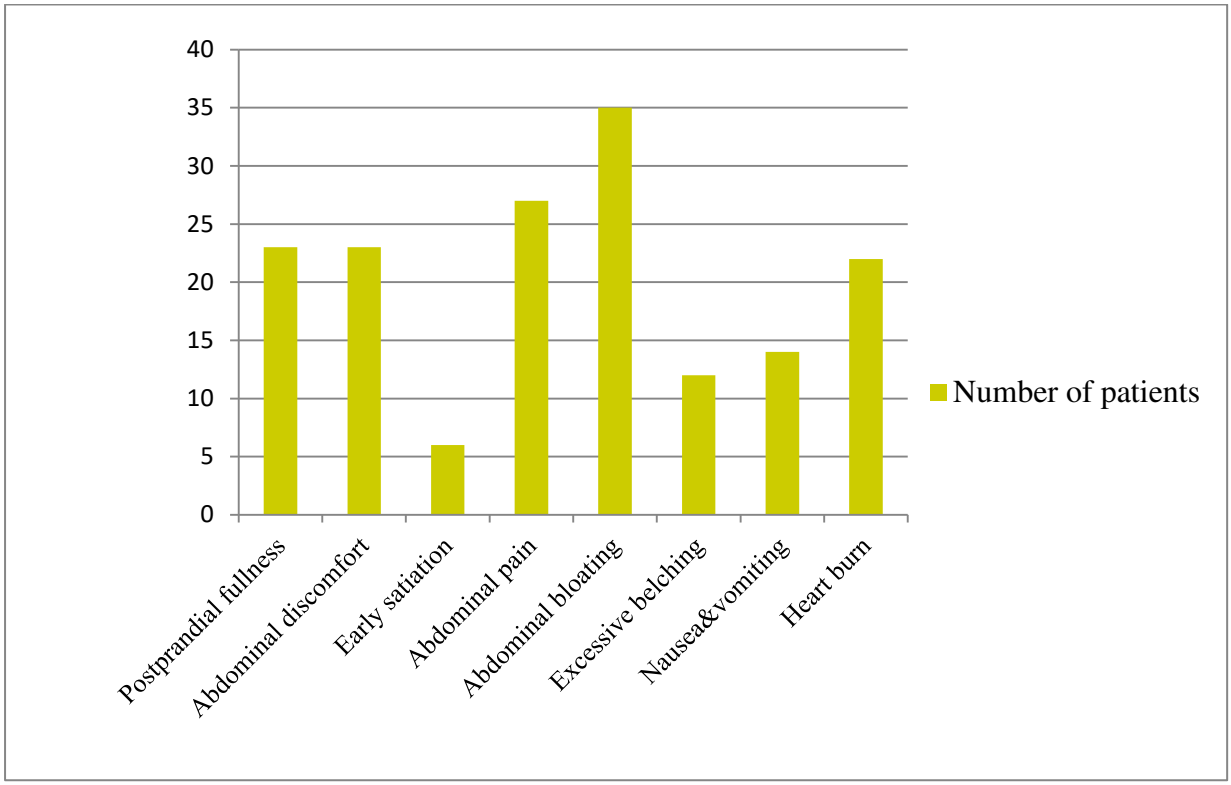

TABLE 9.DISTRIBUTION OF NUMBER OF SYMPTOMS AMONG THE STUDY POPULATION (n=60)

NUMBER OF SYMPTOMS	NUMBER OF PATIENTS(n=0)	PERCENT (%)
1symptom	6	10.0
2symptoms	21	35.0
3symptoms	24	40.0
4symptoms	5	8.3
5 symptoms	3	5.0
7symptoms	1	1.7
TOTAL	60	100.0

FIG.9.DISTRIBUTION OF NUMBER OF SYMPTOMS AMONG STUDY POPULATION (n=60)

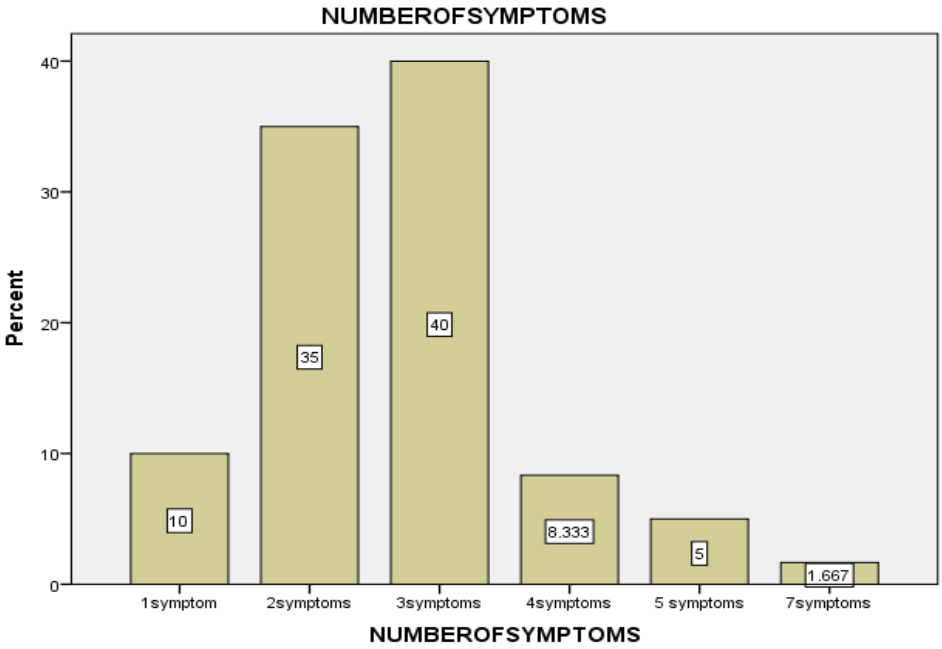

TABLE 10.VISUAL ANALOGUE SCALE SCORE OUTCOMES OF ACOTIAMIDE+PPI THERAPY BEFORE AND AFTER TREATMENT

Symptoms	Acotiamide + PPI therapy(n=20)		
	Before treatment	After treatment	p- value
	Mean ±S.D	Mean ±S.D	
Postprandial fullness	1.20±1.281	0.20±0.410	0.002
Upper abdominal discomfort	0.75±1.333	0.10±.308	0.024
Early satiation	0.25±0.786	0.00±0.000	0.171
Upper abdominal pain	0.90±1.165	0.30±0.470	0.024
Upper abdominal bloating	1.75±1.251	0.35±.489	0.000
Excessive belching	1.35±1.424	0.30±.470	0.001
Nausea& vomiting	0.35±.875	0.05±.224	0.163
Heart burn	0.90±1.410	0.30±0.470	0.042
Total score	2.50±0.827	0.7000±0.47016	0.000

TABLE 11. SUMMARY OF OVERALL AND SUBSCALE SYMPTOM SCORES ON THE SHORT FORM-NEPEAN DYSPEPSIA INDEX(SF-NDI) QUESTIONNAIRE OF ACOTIAMIDE THERAPY BEFORE AND AFTER TREATMENT

Variables	**Acotiamide +PPI Therapy(n=20)**		**P value**
	Before	**After**	
	Mean ±S.D	**Mean ±S.D**	
Tension	2.00±0.649	1.35±0.489	0.001
Interference with daily activities	1.60±0.503	1.20±0.410	0.008
Eating/drinking	1.95±0.224	1.20±0.410	0.000
Knowledge	1.80±0.523	1.25±0.444	0.001
Work/study	2.30±0.470	1.15±0.366	0.000
Total score	2.5500±0.60481	1.0000±0.00000	0.000

TABLE 12. VISUAL ANALOGUE SCALE SCORE OUTCOME OF PPI+DOMPERIDONE THERAPY BEFORE AND AFTER TREATMENT

Symptoms	PPI + Domperidone Therapy(n=60)		
	Before	After	P value
	Mean ±S.D	Mean ±S.D	
Postprandial fullness	1.10±1.294	0.45±0.686	0.033
Upper abdominal discomfort	1.15±1.348	0.40±0.754	0.005
Early satiation	0.25±0.786	0.05±0.224	0.297
Upper abdominal pain	0.90±1.210	0.25±0.550	0.039
Upper abdominal bloating	1.80±1.322	1.25±1.209	0.086
Excessive belching	0.25±0.786	0.15±0.489	0.606
Nausea& vomiting	0.75±1.209	0.65±0.813	0.733
Heart burn	1.20±1.281	0.70±0.865	0.021
Total score	2.4000±0.99472	2.0000±0.56195	0.042

TABLE 13. SUMMARY OF OVERALL AND SUBSCALE SYMPTOM SCORES ON THE SHORT FORM- NEPEAN DYSPEPSIA INDEX (SF-NDI) QUESTIONNAIRE OF PPI+ DOMPERIDONE BEFORE AND AFTER TREATMENT.

Variables	**PPI+ domperidone therapy(n=20)**		**P- value**
	Before	**After**	
	Mean ±S.D	**Mean ±S.D**	
Tension	1.70±0.657	1.75±0.444	0.772
Interference with daily activities	1.65±0.489	1.95±0.224	0.010
Eating/drinking	1.85±0.366	1.95±0.224	0.163
Knowledge	1.65±0.489	1.85±0.336	0.042
Work/study	1.45±0.686	1.80±0.523	0.031
Total score	2.0000±1.07606	1.8000±0.69585	0.428

TABLE 14.VISUAL ANALOGUE SCALE OUTCOMES SCORE OF PPI MONOTHERAPY BEFORE AND AFTER TREATMENT

Symptoms	Proton Pump Inhibitor Monotherapy (n=20)		
	Before	After	P value
	Mean± S.D	Mean ±S.D	
Postprandial fullness	0.65±1.182	0.25±0.786	0.057
Upper abdominal discomfort	1.10±1.410	0.60±1.095	0.047
Early satiation	0.20±0.616	0.20±.616	0.163
Upper abdominal pain	1.40±1.465	0.90±1.165	0.014
Upper abdominal bloating	0.90±1.294	0.55±0.999	0.286
Excessive belching	0.50±1.051	0.55±1.146	0.748
Nausea& vomiting	0.50±1.051	0.40±.995	0.577
Heart burn	1.05±1.356	0.85±1.226	0.104
Total score	2.0500±0.60481	2.2000±0.61559	0.330

TABLE 15. SUMMARY OF OVERALL AND SUBSCALE SYMPTOM SCORES ON THE SHORT FORM-NEPEAN DYSPEPSIA INDEX (SF-NDI) QUESTIONNAIRE OF PPI MONOTHERAPY BEFORE AND AFTER TREATMENT

Variables	**Proton Pump Inhibitor Monotherapy(n=20)**		**P- value**
	Before	**After**	
	Mean ± S.D	**Mean ± S.D**	
Tension	1.35±0.671	1.30±0.733	0.804
Interference with daily activities	1.25±0.099	1.15±0.366	0.163
Eating/drinking	1.45±0.686	1.10±0.069	0.005
Knowledge	1.15±0..366	1.15±0.366	0.000
Work/study	1.40±.681	1.25±0.681	0.419
Total score	1.7000±0.86450	1.4000±0.608056	0.110

6. RESULTS

In this prospective study the management of functional dyspepsia is studied. This study is to assess the therapeutic outcome and quality of life of patients with functional dyspepsia by treating with Proton Pump Inhibitors, Domperidone and a novel prokinetic agent Acotiamide. A total of 70 patients were selected in this study 10 patients were excluded since they were non compliant to the treatment. There by 60 patients with functional dyspepsia were enrolled, who were attending the Gastroenterology Department of Kovai Medical Centre and Hospital during the period of February 2018 to July 2018. Patients were divided into three groups. In each group 20 patients were included. In the first group, patients who received proton pump inhibitors (PPI) alone were included. In the second group patients who undergone PPI and domperidone combination therapy were included. In the third group patients who received combination of acotiamide and PPI were included.

The study population was categorized into 6 groups on the basis of age (Table1).24 patients (40.0%) came under the category of 45 to 54 age group. This indicates that incidence of functional dyspepsia is higher in this population.

Patients were categorized into 2 groups based on gender. 38 (63.3%) patients were coming under the category of male and 22 (36.7%) patients were coming under female category. The results show a male predominance for the disease (Table 2).

Social habits such as alcohol intake, smoking and food habits also related to development of functional dyspepsia. Among the study population (n=60) 96.7 % of patients were not alcoholic (Table.4). 98.3% patients not having smoking habits (Table 3). 37 (61.7%) patients consumed non vegetarian foods. Only 28 (38.3%) patients consumed vegetarian foods. This proves that the people who are consuming non vegetarian foods are more prone to functional dyspepsia.(Table 5).

In this study 30 (50.0%) of patients came under the category of body weight 60-80 which indicates more predominance in development of functional dyspepsia.28 (46.7%) of patients came under 30-80 and only 2 (3.3) of patients came under 80-100 who are less prone to this disease.(Table 6).

Duration of symptoms occurring as a result of dyspepsia differ in individuals while 35 (58.3%) had symptom for 1 month 10 (16.7%) patients had symptoms for 2 months,7 (11.7%) of patients had symptoms for 6 months.5 (8.3%) patients had symptoms for 1 week. Only 3.3% and 1.7% of patients had the symptoms for 1 and 2 years. The duration of symptoms persist about one month for most of the patients (Table 7).

In this study , 35 (58.3%) of patients had upper abdominal bloating,27 (45%) of patients had upper abdominal pain,23 (38.3%) of patients had postprandial fullness and upper abdominal discomfort, 22 (36.6%) of patients had heartburn, only 6(10%) of patients had early satiation and 12(20%) of patients had excessive belching,14 (23.3%) of patient had nausea and vomiting. Abdominal bloating was showed by most of the patients in this study population. (Table 8)

The number of symptoms occurring in each individuals were categorized, 24 (40.0%) patients had three symptoms, 21 (35%) had two symptoms, 5 (8.3%) patients had four symptoms 3 (5%)patients had five symptoms, 6 (10%) patients had one symptom and only 1(1.7%) patients had 7 symptoms. Most of the patients had three symptoms.(Table 9)

Patients were evaluated for the occurance of adverse events caused by treatment found among the study population, almost all patient would not had any serious adverse drug reaction by the treatments. The adverse drug events were analysed with Naranjo adverse drug reaction probability scale (Annexure IV))

By using visual analogue scale (Annexure III), the symptoms of the patients were compared before and after the treatment for each group (Group1- PPI, Group2-PPI + domperidone, Group3- PPI + acotiamide). The symptoms studied were Postprandial fullness, Upper abdominal discomfort, Early satiation, upper abdominal bloating, Upper abdominal pain, Excessive belching, Nausea and Vomiting and Heartburn.

The individual symptoms were studied for each groups. They were evaluated once before the initiation of the therapy and after completion and are shown in (Table 9, 11&13). After acotiamide therapy there was significant decrease in postprandial fullness ($p=0.002$), abdominal bloating ($p<0.001$), upper abdominal discomfort ($p=0.024$), upper abdominal pain

(p=0.024), heart burn (p=0.042), excessive belching (p=0.001). There is significant decrease in the total VAS score (p<0.001).

In the case of postprandial fullness there is a decrease in the symptom score in each group after treatment. Mean score before acotiamide therapy was 1.20±1.281 and after treatment it was 0.20 ± 0.410. There is significant decrease in the symptom (p=0.002), The mean score of symptom before domperidone+PPI therapy was 1.10±1.294 and after treatment it is reduced to 0.45 ± 0.686 (p =0.033). In PPI therapy before treatment the mean score was 0.65 ± 1.182 and after treatment 0.25 ± 0.786 , there is decrease in symptom mean score (p> 0.05).

For upper abdominal discomfort the mean score before and after therapy was 0.75±1.333 and 0.10±.308 respectively, there is significant reduction of symptom after acotiamide treatment (p=0.024). while the mean score before and after domperidone+PPI therapy was 1.15±1.348 and 0.40±0.754 respectively (p=0.005). The mean score of symptoms before and after PPI treatment was 1.10±1.410 and 0.60±1.095 respectively (p=0.047). Upper abdominal discomfort was reduced significantly after treatment for the three treatment.

For early satiation the mean score of symptom before acotiamide treatment was 0.25±0.786 and after it was decreased to 0.00±0.000 respectively (p=0.171), For domperidone +PPI therapy before treatment and after treatment mean score 0.25±0.786 and 0.05±0.224 respectively (p=0.297), For PPI treatment before and after symptom score was 0.05±0.224 and 0.20±0.616 respectively (p=0.163). There is no significant decrease in symptom score before and after therapy in three groups.

In the case of abdominal pain mean score before acotiamide therapy was 0.30±0.470 and after therapy it was reduced to 0.90±1.165 (p=0.024) similarly in domperidone therapy mean score before and after treatment was 0.25±0.550 and 0.90±1.210 (p=0.0390) respectively. In PPI therapy before symptom mean score was 0.90±1.165 and it was reduced to 1.40±1.465 (p=0.014) respectively. There is a significant decrease in the abdominal pain for each group.

For abdominal bloating mean score before acotiamide therapy was 1.75±1.251 and after treatment it was reduced to 0.35±.489 ($p<0.001$).There is significant reduction in the symptom score. But there is no significant reduction in the symptom score in other groups. ((Domperidone $p = 0.086$, PPI $p= 0.286$).

For excessive belching the mean score before and after treatment of acotiamide was 1.35±1.424 and 0.30±.470 respectively. ($p=0.001$) The improvement of symptom scores did not differ significantly for other groups. ($p= 0.606$ for domperidone, $p =0.748$ for PPI). Also there was no any significant improvement of the symptom score for vomiting in three groups.

The patient who treated with acotiamide and domperidone shows a significant reduction in the symptom heart burn shows ($p =0.042$,$p=0.021$) difference between before and after treatment scores .In PPI therapy there is no significant difference in symptom score.($p =0.104$).

In overall the total score of the symptom was reduced in acotiamide and domperidone therapy. ($p<0.001$ and 0.042). While in PPI the overall symptom was not significantly reduced.

By using Nepean dyspepsia index questionnaire, the quality of life of functional dyspepsia patients were compared before and after the therapy between each groups (Table 11,13 &15) .Overall SF-NDI score showed a significant greater improvement from baseline ($p=0.000$), the mean score of overall SF-NDI score before treatment was 2.5500±0.60481 and after treatment was 1.0000±0.00000. Combination of domperidone and PPI and PPI monotherapy did not differ significantly the score between before and after therapy ($p=0.428$,$p=0.110$)

Similarly all the five SF-NDI subscale scores showed improvement from the base line in the acotiamide group compared to other groups.(Tension $p= 0.001$,interference with daily activities $p=0.008$,eating/drinking $p<0.001$,knowledge $p=0.001$,work/study $p<0.001$).

In group II domperidone therapy there is no significant difference in scores of tension, eating/drinking subscale (p=0.772, p=0.163).There is significant improvement in knowledge, interference and work/study subscale scores after treatment.

In group1 PPI monotherapy there is significant improvement in the scores of knowledge and eating/drinking subscale after therapy (p<0.001, p=0.005).There is no any significant improvement in interference (p=0.163), work/study (p=0.419), tension (p=0.804) subscales.

By comparing the visual analogue scale score for each group, most of the symptoms were improved by acotiamide therapy. There is significant improvement in the abdominal bloating, postprandial fullness, abdominal pain, excessive belching , heart burn, upper abdominal discomfort. In combination of domperidone and PPI therapy there is significant improvement in the symptoms of postprandial fullness, upper abdominal discomfort, abdominal pain and heart burn. In PPI monotherapy there is significant reduction in the symptoms of postprandial fullness, upper abdominal discomfort and abdominal pain. The reduction in the overall symptom score was more in the acotiamide treatment group. More symptoms were reduced in acotiamide therapy.

By comparing SF-NDI scores for each groups. A significant reduction in score for all five subscale showed by acotiamide group compared with other groups. By using paired 't' test, compared the overall symptom score and questionnaire score for each groups.

7. DISCUSSION

In this prospective study, out of the total population (n=60), 24 patients (40.1%) came under the category of 45-54 years. In a study **Varsha Narayanan** [46] ***et al.,*** they observed that 60% of the patients were coming under the category of ≥ 40 years which indicates higher incidence of functional dyspepsia with age. Suzanna [12], observed that 26(43%) of patients had higher incidence of FD in age group of 40-60 years. Natasha A. Koloski [47] , observed that mean age of subjects with FGID was 44 yr. This proves that there is an association of age with functional dyspepsia.

In this study population, 38(63.3%) were males and 22(36.7%) were females. In our study males were found more affected than females. Many studies suggest that the incidence of functional dyspepsia is more in females than males. **R.H Jones** [48] ***et al.,*** observed in a study on dyspepsia in England and Scotland that there is a slight excess of female predominance. Roger Jones[49] ,observed in a study of prevalence of functional dyspepsia ,that men and women were represented almost equally.

R. Bitwayiki [31] ***et al.,*** studied the prevalence and quality of life of functional dyspepsia among Rwandan healthcare workers. In this study smoking, use of alcohol were not associated with dyspeptic syndrome. This study shown 39.2% of patients were not smokers 41.9% of patients were not alcoholic. In our study 96.7 % of patients were not alcoholic and 98.3% of patients were not smokers, which indicates smoking and alcohol has not been shown to be a risk factor in our study. However, Yasuhiro Fujiwara [34], observed in their study, that smokers were significantly associated with an increased FD.

K. Matsueda [2] ***et al.,*** also observed that 135(33.3%) of patients came under body weight of 50-60 subgroup. In our study 30 (50.0%) of patients came under 30-60 kilogram of body weight which indicates a higher incidence of FD.

The role of food habit had not been well studied probably due to the diversity of food habits among the individual populations. **Sundeep S Shah** [43] ***et al.,*** observed in a study patients symptoms were worsened after taking non vegetarian diet. Spicy foods,

fried or food prepared outside the home increases the abdominal fullness. In this study the frequency of dyspepsia was not related to the quantity of spices or type of diet (vegetarian or non vegetarian) consumed. In our study 38.3% of patients were vegetarians and 61.7 % of patients are non vegetarians. This study proves that people consuming non vegetarian food are more prone to develop dyspeptic syndromes.

Rocco Maurizio Zagari [50] *et al*., observed in a study of epidemiology of functional dyspepsia and subgroups in the Italian general population, of 114 patients with FD 77(67%) had postprandial fullness and early satiation and 55(48.2%) had epigastric pain. In our study 35(58.3) of patients had abdominal bloating. Most of the patient had abdominal bloating in this study. K.Matsueda [2], observed that among 405 patients 232(57.3%) had postprandial fullness, 94(23.2%) of patients had bloating and 79(19.5%) of patient had early satiation which indicates a predominance in postprandial syndrome in most of the patient.

In our study population, duration of symptoms was different in each individual. 35(58.3%) of the patients had symptoms for 1 month, 5 (8.3%) of patients had symptoms for 1 week, 10(16.7%) of patients had symptoms for 2 months. According to Rome III criteria, the symptoms of functional dyspepsia have a history of 3 months. In our study the duration of symptoms persist for 1 month probably due to life style modification. **Kei Matsueda [4]*et al.***, explained that the duration of symptom for most of the patients ≥1 year.

The overall symptom score for the three groups before and after treatment was documented. The overall symptom score and most of the individual symptom score was reduced after the treatment of acotiamide compared to other two groups (PPI+domperidone, PPI monotherapy). **Kei matsueda[4] et al.,** observed that the symptom score for abdominal bloating, postprandial fullness and early satiation was improved in the acotiamide group compared to placebo. The symptom score for nausea and vomiting, excessive belching abdominal pain, abdominal discomfort did not differ significantly between the groups. In our study there is no significant reduction in the symptom score for early satiation ,nausea and vomiting in the acotiamide group, But had

a significant reduction in overall symptom score and individual symptoms such as postprandial fullness, abdominal bloating, abdominal pain, upper abdominal discomfort, excessive belching, and heartburn. Quality of life of functional dyspepsia patients was also studied by kei matsueda [4]. The overall SF-NDI scores showed a significantly greater improvement after acotiamide therapy. Similarly all five score showed improvement from baseline in the acotiamide group. In our study also there is significant improvement in the overall SF-NDI scores and each five SF-NDI subscale scores in the acotiamide group.

Hiroshi Yamawaki [32] **et al**, observed in a study acotiamide treatment significantly (p=0.007 and p=0.003) improved postprandial fullness and early satiation as PDS symptoms in 4 week treatment compared to those pretreatment.

Satoshi shinozaki [30] ***et al.,*** observed that adherence to a therapeutic regimen with acotiamide therapy improved long-term outcomes in patients with FD. No adverse events occurred throughout the follow up. Long term use of acotiamide is safe and effective, and he also observed the efficacy of acotiamide on epigastric syndrome and postprandial syndrome in another study. It reveals that acotiamide significantly improves the symptoms of EPS as well as PDS at three months.

J. Tack [8] ***et al.,*** observed that long term safety and efficacy of acotiamide in functional dyspepsia postprandial distress syndrome. By evaluating overall treatment outcome each symptom showed a continuous decrease in score from the baseline. For the FD-specific QOL scale SF-NDI the mean value of each domain decreased for all five subscale scores. The eating/drinking domain showed largest decrease in score among five domains. Our study also revealed the same.

In our study by comparing the acotiamide with other two groups, PPI and combination of PPI+domperidone groups, acotiamide showed more improvement in the symptom score and also quality of life score. **Shuhei Mayanagi** [33] ***et al***., observed that the symptom improved after the combination therapy with PPI and acotiamide than PPI monotherapy.

K.Y Marakhouski [12] ***et al.,*** observed in a comparative open label study, omeprazole-domperidone combined therapy demonstrates significantly greater efficacy than omeprazole alone in the treatment of patients with functional dyspepsia and GERD disease. In our study combination of PPI-domperidone combined therapy had significantly greater improvement in symptom score and also SF-NDI score for knowledge, interference and work/study subscale.

This study reveals that potent inhibition of acid secretion had a limited role in the treatment of FD. In our study PPI significantly reduces the symptom score of upper abdominal discomfort and abdominal pain. Based on severity of symptoms, our study also found greater improvement with acotiamide therapy compared to PPI monotherapy.

8. CONCLUSION

Dyspeptic symptoms are defined as the presence of symptoms thought to originate from the gastrointestinal region, occurs commonly in the general population. 20-30% of the general population are affected by this problem. .Functional dyspepsia is characterized by persistent or recurrent epigastric syndromes including postprandial fullness, abdominal discomfort, pain, early satiation, bloating, excessive belching, nausea, vomiting and heart burn.

Our study was focused to assess the therapeutic outcome and quality of life of patients with functional dyspepsia by treating with proton pump inhibitors, domperidone and a novel prokinetic agent acotiamide.

In our study the efficacy of acotiamide was evaluated by comparing with other groups of treatment such as PPI monotherapy and combination of PPI and domperidone. The review on patients with FD after one month showed a significant improvement in acotiamide therapy and PPI + Domperidone therapy. After treatment analysis, revealed more efficacy observed in acotiamide treatment. Similarly SF-NDI score was significantly improved in the acotiamide therapy, All the five domains of SF-NDI were significantly improved after treatment .

Symptoms such as postprandial fullness, abdominal bloating, abdominal pain, abdominal discomfort, excessive belching, heartburn were found to be reduced significantly in acotiamide therapy, and overall symptom score was also reduced significantly. From this study it was concluded that acotiamide has better efficacy than PPI monotherapy, and combination of PPI and domperidone.

Overall study, enabled us to know the efficacy and safety of acotiamide and there by to identify a better treatment option for functional dyspepsia. We believe that our study will provide a guidance for developing more appropriate treatment option for functional dyspepsia.

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ANNEXURE II

DATA COLLECTION FORM

OP. No.: DATE:

NAME: AGE: SEX:

WEIGHT: HEIGHT: BMI:

ADDRESS:

OCCUPATION:

DIET: VEG/ NON-VEG

SOCIAL HABITS – ALCOHOL - present / past / never

SMOKING/ TOBACCO- present / past / never:

PAST MEDICAL & MEDICATION HISTORY:

COMORBIDITIES:

PRESENT COMPLAINTS:

Are you treated before for the same complaints:

If yes which therapy :

MEDICATION REGIMEN

DRUG	**DOSE**	**FREQUENCY**
GROUP I Proton Pump Inhibitor(PPI)		
GROUP II Proton Pump Inhibitor+Domperidone		
GROUP III PPI+Acotiamide		

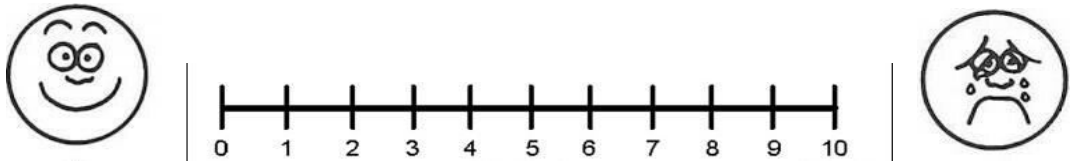
SYMPTOM SEVERITY SCALE:

Sl. No	SYMPTOMS	YES/ NO	DURATION	SEVERITY SCALE			
				NONE (0)	MILD (1)	MODERATE (2)	SEVERE (3)
1	Postprandial fullness						
2	Upper abdominal discomfort						
3	Early satiation						
4	Upper abdominal pain						
5	Upper abdominal bloating						
6	Excessive belching						
7	Nausea& vomiting						
8	Heartburn						

ANNEXURE III

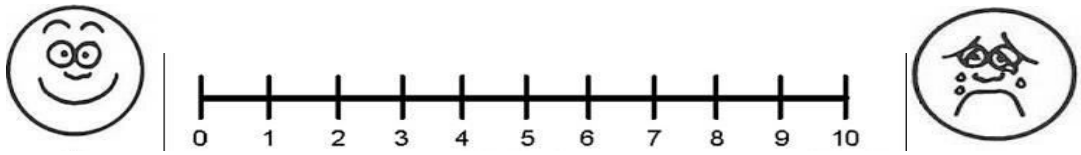
VISUAL ANALOG SCALE (VAS)

Postprandial fullness:



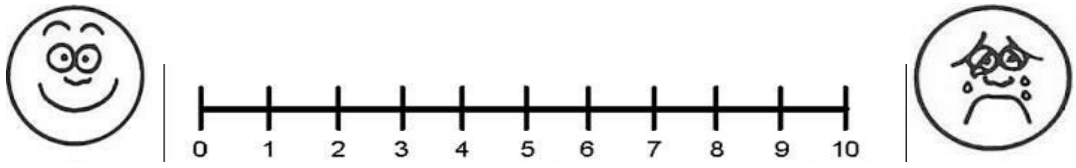
NONE WORST

Upper abdominal discomfort



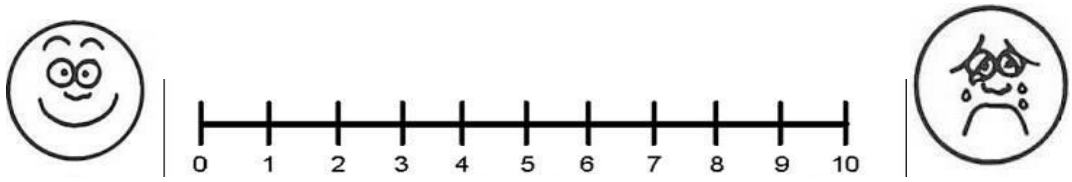
NONE WORST

Early satiation



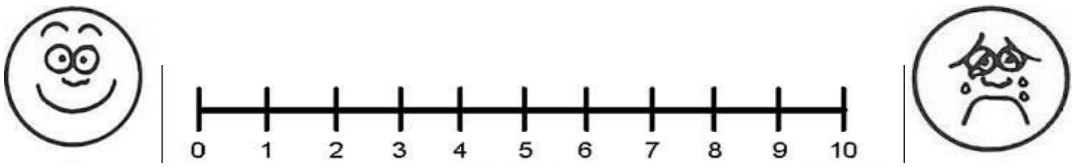
NONE WORST

Upper abdominal pain:



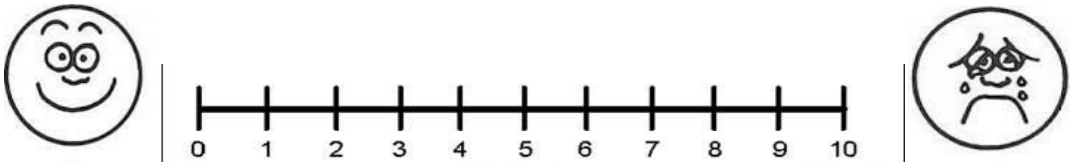
NONE WORST

Upper abdominal bloating:



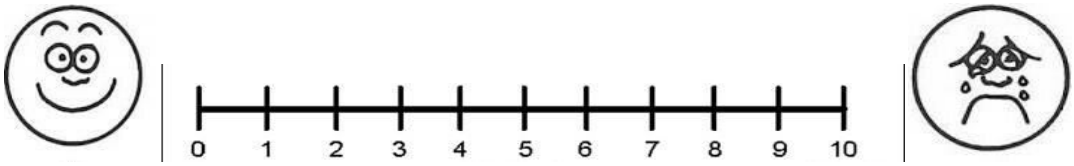
NONE WORST

Excessive belching:



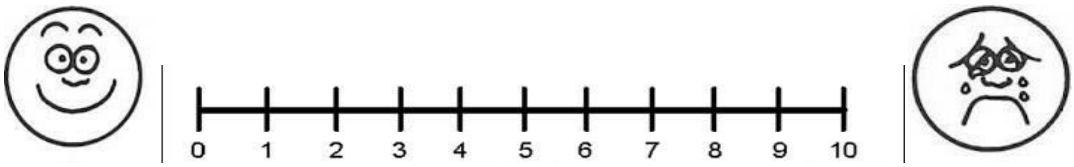
NONE WORST

Nausea& vomiting:



NONE WORST

Heartburn:



NONE WORST

ANNEXURE IV

NARANJO ADVERSE DRUG REACTION PROBABILITY SCALE

NARANJO ADVERSE DRUG REACTION PROBABILITY SCALE					
Sl. No	Question	Yes	No	Do Not Know	Score
1	Are there previous conclusive reports on this reaction?	+1	0	0	
2	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4	Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
5	Are there alternative causes (other than the drug) that could on their own how caused the reaction?	-1	+2	0	
6	Did the reaction reappeared when a placebo was given?	-1	+1	0	
7	Was the drug detected in blood (or other fluid) in concentrations known to be toxic?	+1	0	0	
8	Was the drug more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10	Was the adverse event confirmed by any objective evidence?	+1	0	0	
				Total Score	

Modified from:Naranjo C A et al.Amethod for estimating the probability of adverse drug reactions.Clin Pharmacol Ther 1981;30:239-245.

ANNEXURE V

SHORT FORM DYSPEPSIA INDEX QUESTIONNAIRE (SF-NDI)

Circle the number of the response that best describes how you have been. Each item is scored on a five-point Likert scale (1 = not at all, 2 = a little, 3 = moderately, 4 = quite a lot, and 5 = extremely),

Tension

1. Has your general emotional well-being been disturbed by your stomach problems in the last 2

   weeks?

   1. Not at all.
   2. A little.
   3. Moderately.
   4. Quite a lot.
   5. Extremely.

2. Have you been irritable, tense or frustrated in the last 2 weeks because of your stomach problems?

   1. Not at all.
   2. A little.
   3. Moderately.
   4. Quite a lot.
   5. Extremely.

Interference with daily activities

3. Has your ability to engage in things you usually dofor fun (recreations, going out, hobbies, sports, etc.) been disturbed by your stomach problems in the last 2 weeks?

   1. Not at all.
   2. A little.
   3. Moderately.
   4. Quite a lot.
   5. Extremely.

4. Has your enjoyment of things you usually do for fun (recreations, going out, hobbies, sports, etc.) been disturbed by your stomach problems in the last 2 weeks?
   1. Not at all.
   2. A little.
   3. Moderately.
   4. Quite a lot.
   5. Extremely.

Not applicable (I have not been able to do any of these things in the past 2 weeks)

Eating/drinking

5. Has your ability to eat or drink (including when,what, and how much) been disturbed by your stomach problems in the last 2 weeks?
   1. Not at all.
   2. A little.
   3. Moderately.
   4. Quite a lot.
   5. Extremel

6. Has your enjoyment of eating and/or drinking been disturbed by your stomach problems in the last 2 weeks? (Please also include your appetite, and how you feel after food or drink).
   1. Not at all.
   2. A little.
   3. Moderately.
   4. Quite a lot.
   5. Extremely.

Knowledge/control

7. Have you wondered whether you will always have these stomach problems, in the last 2 weeks?
   1. Almost never.
   2. Sometimes.
   3. Fairly often.
   4. Very often.
   5. always.

8. Have you thought that your stomach problems might be due to a very serious illness (e.g. cancer or a heart problem), in the last 2 weeks?
   1. Almost never.
   2. Sometimes.
   3. Fairly often.
   4. Very often.
   5. always.

Work/study

9. Has your ability to work or study been disturbed by your stomach problems in the last 2 weeks?
   1. Not at all.
   2. A little.
   3. Moderately.
   4. Quite a lot.
   5. Extremely.

   Not applicable (I do not work or study).
10. Has your enjoyment of work or study been disturbed by your stomach problems in the last 2 weeks?
   1. Not at all.
   2. A little.
   3. Moderately.
   4. Quite a lot.
   5. Extremely.

   Not applicable (I have not worked or studied in the last 2 weeks).