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Original Research Article

Randomized Placebo Controlled Single Blind Study of the Effectiveness of Acotiamide in Functional Dyspepsia

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Conflict of interest: Nil

Abstract

Dyspepsia is common disorder with world-wide prevalence. It is derived from the Greek words dys and pepse literally meaning “difficult digestion” which refers to a heterogeneous group of symptoms located in upper abdomen as pain or discomfort centered in the upper abdomen and may include varying symptoms like epigastric pain, post prandial fullness, early satiety, anorexia, belching, nausea and vomiting, upper abdomen. According to the Rome criteria, FD is defined as the presence of early satiety, postprandial fullness, epigastric pain and epigastric burning sensation in absence of organic, systemic or metabolic disease in the setting of a normal upper gastrointestinal endoscopy, abdominal bloating, and even heart burn and regurgitation. Acotiamide a novel GI motility modulator was made available in Japan in June 2013. It’s main pharmaceutical effect is to increase the release of the acetylcholine ligand from cholinergic nerve terminals by inhibition of acetylcholinesterase [9] .It also antagonizes M1 and M2 muscarinic receptors that modulate Acetylcholine release. It also has gastroprokinetic activity, it has been shown to have beneficial effects mainly for improving meal related symptoms such as postprandial fullness, upper abdominal bloating or early satiation without any major side effects. Study subjects were recruited from the General Medicine OPD of College of medicine and Sagore Dutta hospital, Kamarhati. Adult subjects (18-55 years) of either sex, complaining of dyspepsia for at least 1 month and without having any abnormal pathological finding in upper GI endoscopy were included. Subjects who are taking drugs that might cause dyspepsia symptoms and those with serious concomitant disease of vital organs or alarm symptoms (as example-risk of gastroesophageal malignancy or other serious gastrointestinal disorders), were excluded. Subjects were randomized to receive either Acotiamide 300 mg or placebo drug once daily before lunch. Drugs were administered in single blind manner. Treatment was continued for a total period of 4 weeks and subjects would be assessed at the end of 2nd and 4th weeks. Target sample size was 35 patients per group, adjusting for dropouts. The primary objective of this study was to determine the efficacy of Acotiamide in relieving symptoms of dyspepsia by using Global Overall Symptom Scale and Quality of life (QOL) Questionnaire. Effectiveness of drug was assessed by Global Overall Symptom Scale. For each symptom, relief would be taken as a score or 3 or less and resolution as a score of 1 or less. Quality of life assessed by SF8 QOL questionnaire and improvement of score denotes improvement of quality of life. The secondary objective was to assess the Safety Profile of the drug when used chronically in Indian population over a 4 weeks period. Standard biochemical test parameters and treatment emergent adverse events would be recorded as safety variables. It is found in the study that the drug Acotiamide has more effectiveness over the period of 4 weeks as compared to placebo in the patients suffering from functional dyspepsia, and it has been shown in this study that Acotiamide decreased the different symptoms component of functional dyspepsia as measured by global overall scale. It has been seen that quality of life score also increased significantly post treatment compared to pretreatment in Acotiamide group. The limitations of the study was its short duration for only 4 weeks for which long-term follow-up for various adverse events cannot be done. Another limitation of the study was small number of study subjects.

Conclusion: From this study this conclusion can be made that, Acotiamide, the newer gastro motility inducer, is found to be beneficial for relieving different symptoms in the patients suffering from functional dyspepsia compared to placebo. It can be used in such patients effectively.

Introduction

FD is a clinical syndrome comprising chronic symptoms arising from the gastroduodenal region[1] According to the Rome criteria, FD is defined as the presence of early satiety, postprandial fullness, epigastric pain and epigastric burning sensation in absence of organic, systemic or metabolic disease in the setting of a normal upper gastrointestinal endoscopy[2]. Actually dyspepsia symptom complex are broader than the 4 cardinal symptoms that constitute ROME III [5] definition. It includes multiple symptoms like epigastric pain, early satiation, bloating, epigastric burning, postprandial fullness, nausea, vomiting, belching etc. weight loss is traditionally considered as an alarm symptoms.

Dyspepsia is derived from the Greek words dys and pepse and it literally means “difficult digestion”. In current medical terminology dyspepsia refers to a heterogenous group of symptoms located in upper abdomen. In the Indian population, dyspepsia has been reported to be more common in subjects aged 40 years or younger.[3] It is more prevalent in the metros where it is reported by almost one-third of the population.[4] According to the ROME III & updated ROME IV criteria functional dyspepsia is defined as the presence of bothersome symptom(postprandial fullness, early satiation, epigastric pain, epigastric burning etc)that are unexplained after routine clinical evaluation . [5,6] Empirical therapy with antacids, antisecretory and prokinetic agents was the traditional approach for most physicians in the initial management of patients with functional dyspepsia[7] . Symptoms needed to be present for 4 weeks and needed to include upper abdominal pain or discomfort or heartburn, acid reflux, nausea and vomiting etc.

Acotiamide is a first-in-class drug having prokinetic activity by enhancing acetylcholine release by acting as an antagonist on muscarine auto-receptors in enteric nervous system. It also acts by inhibiting acetylcholinesterase activity.] In some trials which were conducted in, USA ,Japan and Europe, Acotiamide has been shown to have somewhat beneficial effects particularly for improving post meal dyspepsic symptoms like post prandial fullness, early satiation ,upper abdominal bloating without no major side effects. [8-11] There are no published reports from eastern India about the effectiveness of acotiamide in functional dyspepsia or in the treatment of acid-peptic disorders. We therefore decided to conduct a randomized single blind placebo controlled study to examine it in functional dyspepsia.

The primary objective of this study is to determine the efficacy of Acotiamide in relieving symptoms of functional dyspepsia by using Global Overall Symptom Scale and Quality of life (QOL) Questionnaire. The secondary objective is to assess the Safety Profile of the drug when used chronically over a 4 weeks period.

Materials and Methods

This study was registered in CTRI, trial number is REF/2022/07/056204.The study commenced only on approval of Institutional Ethics Committee. It conformed to the Declaration of Helsinki for biomedical research involving human subjects and every effort would be made to adhere to GCP GUIDELINES OF Govt of India for clinical research and according to the new drug and clinical trial rules. This is an experimental, prospective, single blind, randomized controlled parallel group study which was done in General Medicine OPD in College of Medicine and Sagore Dutta Hospital.

Inclusion Criteria:

1. Adult subjects (aged between 18 to 55 years)
2. Symptoms of dyspepsia for at least 1 month
3. Upper Gastrointestinal Endoscopy without any pathological findings

Exclusion Criteria:

1. Patients with abnormal upper GI endoscopy
2. Patient with alarm features (unintentional weight loss, persistent vomiting, dysphagia, hematemesis, melena, fever, jaundice, or anemia)
3. History of recent gastrointestinal surgery i.e. within 30 days
4. Patients who show any of the following values at the baseline laboratory tests:

a) Severe Anemia (Hb%≤7gram/dl)
b) Total Leukocyte Count <3,000/mm^3,
c) Platelet count < 75,000/mm^3,
d) AST and ALT ≥ 100 IU/L,
e) Creatinine ≥ 1.5 mg/dl,

5. Treatment with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), H2-blockers, proton pump inhibitors, prokinetic agents,

misoprostol or sucralfate 15 days prior to enrollment
6. Concomitant serious disease of vital organs such as the liver, kidney, heart or lungs
7. History of hypersensitivity to either of the study drugs or closely allied drugs
8. Pregnant and Lactating woman

Sample size calculated in each group in order to detect 75% responder in acotiamide arm and 50% responder in placebo arm with 80% power and 5% probability of type I Error IS 31. Considering 10% dropout total sample size in each arm is 35.

Symptoms of dyspepsia i.e. abdominal pain, acid regurgitation, heart burn, nausea & vomiting, abdominal distention, borborygmus & eructions, early satiety & postprandial fullness are to be assessed by Global Overall Symptom Scale (7 point Likert scale)[12,13].A patient reporting at least moderate severity (score ≥4) for an individual symptom would be considered to be symptomatic for that specific symptom. Reassessment will performed at the end of second week (Day14) and forth week (Day28). For each symptom, relief would be taken as a score or 3 or less and resolution as a score of 1 or less. Quality of life score over 4 weeks by SF-8 scale in both physical and mental component score.

Treatment associated adverse events were reported spontaneously by study subjects and noted by investigators during taking history and basic clinical examinations at each visit. Blood parameters like hemoglobin, total and different leucocyte counts, fasting blood glucose level, platelet count, kidney and liver function tests were done twice- at baseline and after 4 weeks treatment. Tablet acotiamide 300 mg was administered by oral route one time a day before meal as test drug. Placebo drug (dummy medication looks alike test drug which contained vitamin B Complex) was administered once a day by oral route.

Result and Discussion

Out of the 70 patients randomized to be included in the study (35 patients received placebo drug and 35 patients received acotiamide) 68 patients completed all the visits. 2 patients (1 in Placebo group and 1 in Acotiamide group) completed 1st visit at 2nd week but not attend the final visit, so the finding of 1st visit is carried forward to final visit (intention to treat). Among all the analysed subjects 35 were in placebo group and 35 in acotiamide group, of these subjects 24 subjects in acotiamide group were male, on the other hand 17 subjects in placebo group were male. Overall Symptoms were assessed by GOS score the proportion of patients who achieved symptom resolution, and symptom relief for the overall severity of their dyspeptic symptoms in each treatment group. At the end of week 2 and week 4, the proportion of patients who achieving symptom relief (GOS ≤2) and symptom resolution (GOS=1) was shown. Patients in both the treatment group showed significant increase in quality of life assessment by SF-8 score (p <0.001) in comparison between baseline value and end of study value) in quality of life score over 4 weeks in SF-8 scale in both physical and mental component score. Pretreatment characteristics were analysed as per Kolgomorov- Smirnov test of normalcy which shows all the distribution is parametric except GOS. Demographic age, weight, compared as per student unpaired t-test and gender compared using chi square test.

In this present study mean age of acotiamide group was 38.71+-11.23 and placebo group was 37.86+-9.51 ranging from 18 to 55 years in both group. There was no significant difference between two groups in screening or baseline visit regarding demographic characteristics as well as analyzing parameters. For acotiamide arm, one way anova bonferroni test within visits (baseline vs first follow up vs end visit) is significant (<0.05). For placebo arm one way anova bonferroni test within visits (baseline vs first follow up vs end visit) is non-significant. Present study showed that there was significantly (<0.05) decrease in GOS score (mean 3) in first follow up visit (at 2 weeks) than the baseline visit in acotiamide group whereas the score remained same (mean 4) in placebo group. At end visit (at 4 weeks), there was decrease in GOS score compared to 1st follow up visit in acotiamide group compared to placebo group (p<0.05).

At end visit, there was improvement of QOL score (both physical and mental component) than baseline visit compared to placebo group (p value<0.05).

Masclee et al [14] also showed in A dose ranging, placebo controlled, pilot trial of Acotiamide in patients with FD, that there was significant improvement of QOL score(physical component) as well as overall symptom score with Acotiamide compared to placebo group.

A Phase III trial [15] was conducted as a randomized, double-blind, placebo-controlled, parallel-group comparative study, which examined the advantages of the placebo effect on patients who had the following symptoms like postprandial fullness, upper abdominal distension, and early satiation. Acotiamide improved symptom severity and quality of life score as well as meal related symptoms were relieved as compared to placebo.

The present study also showed that there were no significant difference of blood parameters (Hb, TLC, SGOT, SGPT, ALP, UREA, CREATININE) at end visit compared to baseline visit in both group(p value>0.05).No adverse event were

reported in both group. No rescue medicine was added. Home medications were continued which were being taken by subject before initiation of trial.

Limitation of the study: The study was conducted on a small number of study subjects so adverse events in long term follow up for adverse events could not be done. It could have been better if the study was done over long term period.

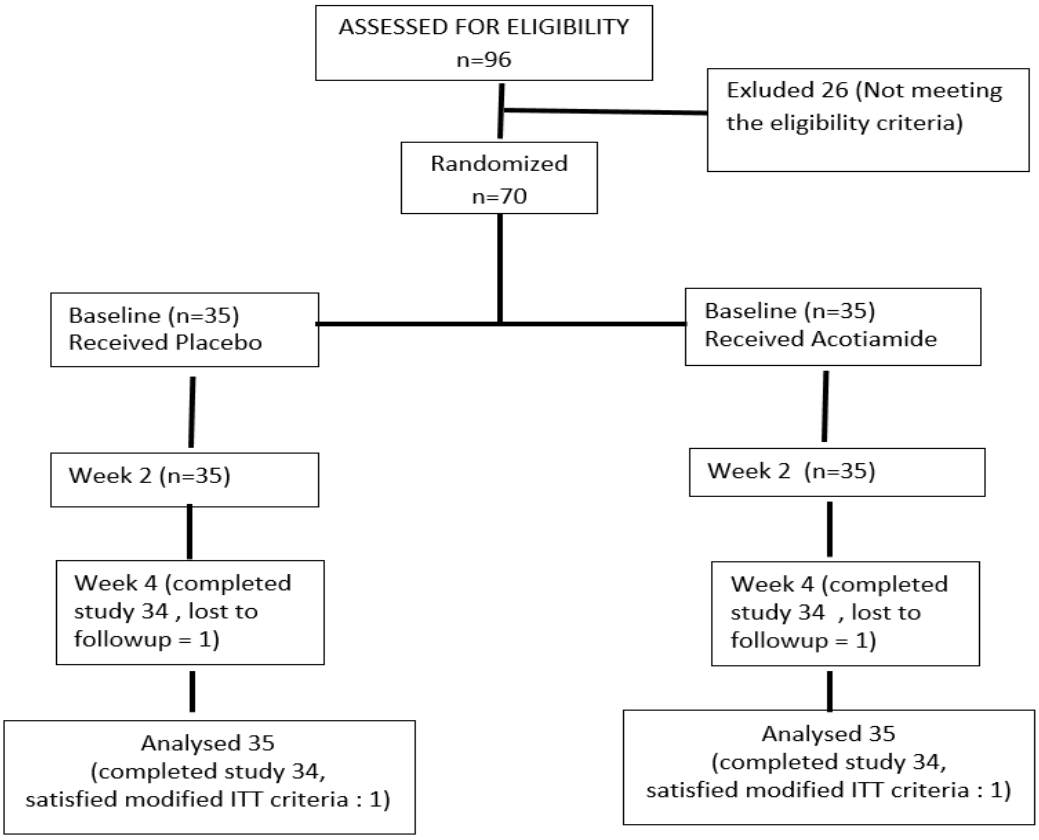

Figure 1: Consort Diagram Depicting Flow of Patients in Both The Arm

Table 1: Baseline demographic characteristics in both the arm

	Acotiamide (n=35)	Placebo(n=35)	P value
Age	38.71+-11.23	37.86+-9.51	0. 732
Weight	61.35+-9.75	59.75+-10.52	0.396
Gender	Male – 24	Male – 17	0.145
	Female – 11	Female – 18	
GOS(median IQR)	4(4-5)	4(4-5)	0.314
SF8MCS(mean +-SD)	41.06+-3.19	40.57+-2.64	0.692
SF8PCS(mean+-SD)	40.54+-5.92	40.77+-3.49	0.788

Abbreviations: GOS=Global overall symptoms Scale; SF-8 MCS=Quality of life SF-8 Mental Component Summary; SF-8 PCS=Quality of life SF-8 Physical component summary

Table 2: Baseline demographic characteristics in both the arm

SCORE	Acotiamide	Placebo	p-value
GOS(median IQR)	2(1-3)	4(4-5)	<0.05
SF8MCS(mean +-SD)	46.29+ 2.92	38.77+2+ 2.85	<0.05
SF8PCS(mean+-SD)	46.8+ 3.64	39.11+ 2.42	<0.05

Abbreviations: GOS=Global overall symptoms Scale; SF-8 MCS=Quality of life SF-8 Mental Component Summary; SF-8 PCS=Quality of life SF-8 Physical component summary

Table 3: Comparison for GOS AND SF8 scores in the Acotiamide arm from baseline Visit and subsequent visit

Scores	Baseline Visit	1ST FU	End Visit	P-Value
GOS(median IQR)	4(4-5)	3(2-3)	2(1-3)	<o.o5
SF8MCS(mean +-SD)	41.06+-3.19	---	46.29+ 2.92	<0.05
SF8PCS(mean+-SD)	40.54+-5.92	---	46.8+ 3.64	<0.05

Abbreviations: GOS=Global overall symptoms Scale; SF-8 MCS=Quality of life SF-8 Mental Component Summary; SF-8 PCS=Quality of life SF-8 Physical component summary

Table 4: Comparison for GOS AND SF8 scores in the Placebo arm from baseline Visit and subsequent visit.

Scores	Baseline Visit	1ST FU	End Visit	P-Value
GOS(median IQR)	4(4-5)	4(4-5)	4(4-5)	>0.05(BSvsF1:0.558)(F1vsE:0.740)
SF8MCS(mean +-SD)	40.57+-2.64	---	38.77+2+_2.85	0.327
SF8PCS(mean+-SD)	40.77+-3.49	---	39.11+_2.42	0.250

Abbreviations: GOS=Global overall symptoms Scale; SF-8 MCS=Quality of life SF-8 Mental Component Summary; SF-8 PCS=Quality of life SF-8 Physical component summary

Figure 2F

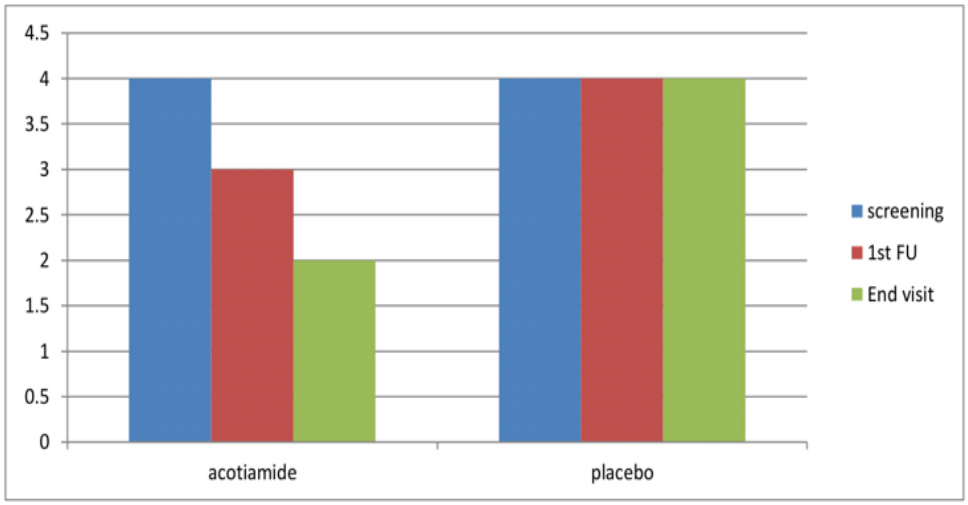

Figure 2: Bar diagram showing GOS scores of 3 visits. GOS = Global Overall Symptoms;

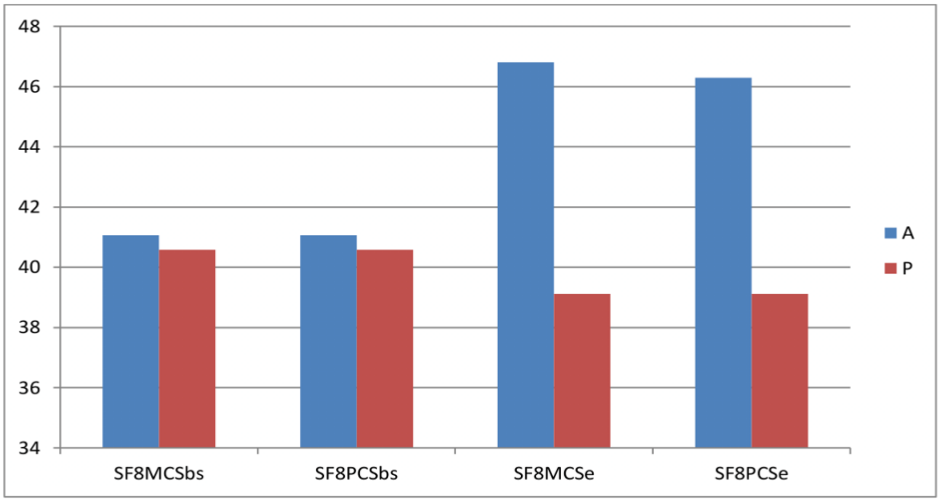

Figure 3: Bar diagram showing SF8 quality of life score of screening and end visit.

For acotiamide arm, one way anova bonferroni test within visits (screening vs first follow up vs end visit) is significant (<0.05). For placebo arm one way anova bonferroni test within visits (screening vs first follow up vs end visit) is not significant. Abbreviations: SF-8MCSbs=Quality of life SF-8 Mental Component Summary baseline score; SF-8 PCSbs=Quality of life SF-8 Physical component summary baseline score, SF-8MCSe=Quality of life SF-8 Mental Component Summary end of study; SF-8 PCSe=Quality of life SF-8 Physical component summary end of study. A=ACOTIAMIDE ARM, P=PLACEBO ARM

Conclusion:

The main aim of this study is to assess the efficacy of Acotiamide in functional dyspepsia, a common clinical entity and secondarily to note its adverse event profile in Indian population presenting at Medicine OPD in a tertiary care hospital in eastern India. The primary objective of this study was to determine the efficacy of Acotiamide in relieving symptoms of dyspepsia by using Global Overall Symptom Scale and Quality of life (QOL) Questionnaire. The secondary objective was to assess the Safety Profile of the drug when used chronically in Indian population over a 4 weeks period. From this study this conclusion can be made that, Acotiamide, the newer gastro motility inducer, is found to be beneficial without any noticeable severe adverse event for relieving different symptoms in the patients suffering from functional dyspepsia compared to placebo. It can be used in such patients effectively.

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