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Observational Study on Comparison of Efficacy and Eradication Rate of Two Anti *Helicobacter pylori* Regimens in Patients with Acid Peptic Disorders

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ABSTRACT

Overall lifetime prevalence of Acid Peptic Disorder (APD) is around 10-20%. In India itself, antacids and antiulcer drugs share 6.2 billion rupees and occupy 4.3 % of the marketed share. Mostly patients of acid peptic disorders are infected with H. pylori. Lafutidine is a novel H2-receptor antagonist with the gastroprotective activity that includes enhancement of gastric mucosal blood flow. The present study was intended to compare the effectiveness of 14-day, Lafutidine-Clarithromycin- Amoxicillin therapy with the Esomeprazole Clarithromycin-Amoxicillin therapy for H. pylori eradication. Patients with H. pylori-infected APD were randomly enrolled for two regimens Esomeprazole (20 mg b.i.d.), Clarithromycin (500 mg b.i.d.), and Amoxicillin (1000 mg b.i.d.) and Lafutidine (10 mg b.i.d.), Clarithromycin (500 mg b.i.d.) and Amoxicillin (1000 mg b.i.d.) for 14 days. The comparison of the effectiveness of the two regimens was done by faces pain scale, endoscopic grading, and symptom scoring, and eradication rate was checked by the rapid urease test. Willcoxon matched pair test was used for statistical analysis.

1. INTRODUCTION

"Acid Peptic Disorder "(APD) is a collective term used to include many conditions such as gastroesophageal reflux disease (GERD), gastritis, gastric ulcer, duodenal ulcer, esophageal ulcer, Zollinger Ellison Syndrome (ZES) and Meckle's diverticulum ulcer. It is a common disorder of the community with an overall lifetime prevalence of around 10-20%. It causes significant morbidity and mortality and death occurs as a consequence of complicated peptic ulcer disease. [Kuipers et al., 1995] This disease is a perennial problem encountered by clinicians around the world, with direct and indirect health care costs of ~$10 billion per year in the United States. In India itself, antacids and antiulcer drugs share 6.2 billion rupees and occupy 4.3 % of the marketed share [Kalyanakrishnan and Robert, 2007]. Both duodenal and gastric ulcer diseases are closely associated with Helicobacter pylori (H. pylori) infection. Over 80-95% of patients of duodenal ulcer/peptic ulcer disease patients are infected with H. pylori [Kreiss et al., 1995].

"H. pylori have since been defined by WHO as class -1 carcinogen." The H. pylori infection is also linked with the development of non-cardiac gastric adenocarcinoma. The risk of gastric cancer was six times greater in H. pylori-infected than in uninfected persons [Suerbaum and Michetti, 2002]. Interfamilial spread of the infection has been well documented. Medical personnel are high-risk groups and gastroenterologists have a higher prevalence of infection when compared to their other medical colleagues [Lambert, 1994]. The imbalance between the aggressive factors & local mucosal defensive mechanisms causes this disease [Herfindal and Dick, 2000].

Genetic factors also play an important role in both duodenal and gastric ulcers. The first-degree relatives of patients with duodenal and gastric ulcers have a two to three-fold increased risk of getting duodenal and gastric ulcers [Kurata and Haile, 1984]. Recent studies show that people with type O blood are the ones most likely to suffer horrible burning when they are infected with H. pylori [Evwrth et al., 2000].

Three antibiotics have drawn special attention for H. pylori management i.e. Clarithromycin, Amoxicillin, and Metronidazole [Lind et al., 2000]. Clarithromycin, a Macrolide antibiotic, has an antimicrobial spectrum similar to that of erythromycin, but it is better absorbed, has better acid stability and tissue penetration, and is concentrated in the mucosa and mucus layer. In humans, Clarithromycin is metabolized to its chief metabolite, 14-OH

Clarithromycin, which is two times more active, and its MIC value decreases 10-fold with increasing pH. Amoxicillin is frequently preferred in H. pylori eradication since almost no resistance develops. So, patients require taking the best drug regimen for complete eradication of H. pylori infection [Koivisto et al., 2008]. Triple drug regimen is having an excellent eradication rate with good ulcer healing capacity [De Idiaquez et al., 1999]. Triple and quadruple therapies seem to be roughly equivalent in terms of effectiveness, compliance, and side-effects profile when administered as first-line treatment for H. pylori infection. Even for triple-drug therapy in a country like India cost consideration is most important, because of the mentioned advantages and relatively lower rate of adverse effects in comparison with the regimens containing Metronidazole or Bismuth [Gene et al., 2001].

Esomeprazole is the most potent drug among all proton pump inhibitors (PPI). It also posses antibacterial activity. The MIC50 and MIC90 of Esomeprazole were 16 and 32 mg/L [Vergara et al., 2003]. Though PPI based triple-drug regimen is considered as standard drug regimen for H. pylori treatment, but 20% recurrence occurs with PPI based triple therapy. Secondly proton pump inhibitors such as Omeprazole and Lansoprazole are mainly metabolized by CYP2C19 in the liver. The therapeutic effects of proton pump inhibitors are assumed to depend on CYP2C19 genotype status. [Luigi 2003].

PPIs may interact with certain drugs, including phenytoin, diazepam, warfarin, digoxin, and clopidogrel [Stedman and Barclay, 2000]. Long-term use of high-dose PPIs may also produce vitamin B12 deficiency [Norgard 2009]. Drugs that depend on stomach pH for absorption further interact with Omeprazole [Rossi 2008]. Amoxicillin-Clarithromycin and esomeprazole combination regimen is the most frequently preferred in our country as well as throughout the world.

The ideal medication for gastric acid-related diseases should have a rapid onset of action and longer duration of action. Lafutidine is a highly potent drug among all antihistaminic drugs. It has 20-80 times high affinity to bind histamine receptors. It gives a rapid onset of action and longer duration of action [Dobrucali et al., 1998].

Lafutidine causes a sustained increase in intracellular Ca+2 ion concentrations in endothelial cells, which induces the release of CGRP, subsequent stimulation of nitric oxide [NO] production to regulate gastric mucosal blood flow through vasodilatation of gastric microvasculature. Also CGRP released from afferent neurons in the gastric mucosa

stimulates D cell in the antral and fundic glands and leads to an increase in somatostatin which directly acts on somatostatin receptor on parietal cells, and indirectly act on antral G-cell which decreases the release of gastrin [Tomohiko 2010]. Lafutidine has muco-protective action in addition to antisecretory action through capsaicin-sensitive afferent nerve plays an important role in gastric mucosal defence mechanism. Lafutidine mimics the endogenous effects of prostaglandins to augment the gastric mucosal blood flow. By this mechanism, helps to washout aggressive bacteria [Higuchi et al., 2006]. Lafutidine increases mucus secretion and thickness by incorporating glucosamine. Lafutidine enhances nitric oxide-mediated biosynthesis of mucus [Kato et al., 2000].

Further lafutidine inhibits H. pylori adherence to gastric epithelial cells and protects against the mucosal inflammation associated with H. pylori infection [Bhupesh 2010]. Lafutidine also inhibits H. pylori-induced interleukin-8 production in human gastric epithelial cells [Ichikawa et al, 1998]. Lafutidine-based triple therapy has been studied in China and was found to be effective for H. pylori infection, and could hence be considered as an additional treatment option [Nozawa et al., 2004].

However, very few studies are available in India showing the comparison of efficacy and eradication rate of various combination regimens in anti H.pylori regimen in patients with acid peptic disorder and hence we aimed to compare the two-drug regimens.

Objectives:

The objective of the study was to find out the prevalence of Acid peptic disease according to age, gender, status, and endoscopic finding. The second objective was comparison of efficacy of two Anti H. pylori drug regimen 1 (Esomeprazole, amoxicillin, and Clarithromycin) with regimen 2 (Lafutidine, amoxicillin, and Clarithromycin) in patients of peptic ulcers. And to compare the eradication rate of H. pylori in APD patients.

MATERIALS AND METHODS

Ethical Review Procedure:

The study protocol, case record form, and informed consent forms [ICFs (English, Gujarati)] along with other submitted documents were reviewed and approved by the Institutional Human Research Ethics Committee in a meeting[IHREC]. [Appendix 1]

Informed Consent Form and Case Record Form:

ICF was prepared in English as well as a vernacular language [Gujarati]. [Appendix 2]

CRF was prepared to include all personal and disease-related details. [Appendix 3]

Study Design:

The proposed study was Prospective, cohort, and observational type.

Study Site:

Patients were enrolled from Gastro Care Clinic and endoscopy center, Rajkot, Gujarat, India.

Inclusion and Exclusion Criteria:

Inclusion criteria:

A) Patients of either sex and above 18 years of age were included in the study.

B) Patients meeting the criteria for acid - peptic disorders (APD)/peptic ulcer disease (PUD) as defined by the presence of all the following:

C) Patients suffering from Epigastric pain for at least 3 days with APD/PUD, with the presence of H. pylori and not effectively controlled with the standard modern scientific treatment were included in the study.

D) Endoscopies performed within 4 days before test drug therapy in patients who revealed visible excoriations of mucosa and not more than 3 active peptic /duodenal ulcers or areas of inflammation were included in the study.

E) All the patients who are willingly signing the written informed consent document.

Exclusion criteria:

A) Patients with secondary complications such as bleeding ulcers, pyloric stenosis, etc.

B) Patients who received the standard anti-ulcer treatment (H2 receptor antagonist and proton pump inhibitors) in the previous 2 weeks and /or herbal medicines in the previous 2 months were excluded.

C) Patients receiving concomitant non-steroidal anti-inflammatory drugs and steroids.

D) Patients with prior gastric surgery.

E) Patients with chronic alcoholism /drug abuse.

F) Pregnant, lactating females.

G) Patient whose endoscopic findings revealed mucosa with more than three ulcer, erosion/punctures /fresh clots at the ulcer sites/cancerous growth/any other mucosal abnormality were excluded also Patient suffering from any severe adverse reaction due to other morbid condition were also excluded [Onodera et al., 2004].

Selection and Enrolment of Patients:

90 patients were randomly and equally divided and enrolled in the study as per the clinician's decision including 45 patients in each group.

Dosage and Frequency: [Pendley et al., 1993].

Group 1 received Amoxicillin 500mg capsule b.i.d. + Esomeprazole tablet 20mg b.i.d. + Clarithromycin 250 mg tablet b.i.d.

Group 2 received Amoxicillin received 500mg capsule b.i.d. + Lafutidine 10 mg tablet b.i.d. + Clarithromycin 250 mg tablet b.i.d.

(If aggravation of clinical symptoms occurs; the rescue medication was prescribed by the consulting gastroenterologist and was recorded in the CRF).

Duration of Study:

Treatment was given for 14 days and the study was carried out from December 2012 to March 2013.

Investigational Parameter:

Baseline Evaluation:

A) Prior screening: the patients were explained about the study procedures.

B) Written informed consent was taken.

C) At baseline visit the medical history; general and systemic examination, details of previous anti-ulcer therapy, and other concomitant medication were recorded in record form (CRF).

Assessment of Effectiveness:

Clinical parameters [refer appendix 3] (were evaluated based on gradation and facial analog scale).

Assessment of Effectiveness by Endoscopic Method:

The effectiveness rate was graded using the endoscopic examination to get more ideas about types of APD. Observation of Esophagus, Stomach, and Duodenum was examined and graded as normal (0), low grade (1), moderate grade (2), severe grade (3).

Assessment of Effectiveness by Symptom Score Method:

The effectiveness rate was also graded using a symptom scoring method to evaluate the severity of the symptoms like vomiting, haematemesis, belching, Malena, bloating, regurgitation, and level of appetite. A grading was given as none (0), mild (1), moderate (2), severe (3).

Assessment of Effectiveness by the Faces Pain Scale Method:

The effectiveness rate was graded using a facial analog scale. So, patients can easily correlate with the expressions of the faces given and can give more precise grading from 0 to 10. Such symptoms included Epigastric pain (day), epigastric pain (night), heartburn, nausea, dyspepsia. 0 scale was given for no effect while 10 is given to represent maximum imagined effect [Wong and Rahwan, 1990].

Assessment of eradication of H. pylori:

The eradication rate was assessed using Rapid Urease Test Kit. The test was carried out at 0 day and 14th day of the treatment. Based on observation eradication rate was assessed, as pink color gave confirmation of H. pylori-positive and persisting yellow color after 30 mins, indicated the patient to be H. pylori-negative.

Evaluation Schedule:

Patients were followed up on the 7th and 14th day for the general and systemic examination and recording of clinical investigation parameters.

Figure 1 Faces Pain Scale

Statistical Analysis:

All the data were analyzed using the willcoxon matched pair test. The CIs (confidence interval) was set at 95% for differences in the among two study groups and were calculated using standard methods. p-values of < 0.05 were considered statistically significant [Nozawa et al., 2004].

RESULT AND DISCUSSION:

For H. pylori eradication, there has been always a question of whether PPIs are superior or H2-receptor antagonists [Gisbert, et al., 2003]. However some systemic review and meta-analysis including published randomized studies showed an overall greater efficacy of PPIs compared to H2-receptor antagonists for the eradication rate of H. pylori. [Nayoung, et al., 2008].

Lafutidine (LFT) is the most recent H2-receptor antagonist used in clinical practice; it has been reported to be more potent and to have longer-lasting H2--receptor blocking activity. In addition to its antisecretory activity, LFT also has gastroprotective effects and increased GMBF and delivery of antibiotics to the gastric mucosa. [Koivisto, T.T., et al., 2008]. Further, very few studies are available in India showing comparative effectiveness and eradication of various combination regimens.

Therefore, we observed the comparison of efficacy and eradication of Lafutidine-clarithromycin–amoxicillin regimen and Esomeprazole-clarithromycin–amoxicillin regimen in H. Pylori related APD.

Study Flow and Overall Compliance:

The schematic diagram of the study protocol is mentioned in figure 2. Ninety patients with H. pylori-infected peptic ulcer diseases were enrolled [mean age, 35.20 years; above 18 years]. The demographic and clinical characteristics of the two study groups are summarized further.

No significant difference was observed between the two groups for demographic or clinical characteristics. Eighty of the ninety patients completed their allocated regimens, and the remaining 10 dropped out [Figure 2]. Specifically, 4 patients did not come for follow up study while 1 patient was drop out due to noncompliance in the EPZ group; whereas 3 patients did not come for follow up study while 2 patients were dropped out due to non-compliance in the LFT group. There was no significant difference in these dropout rates.

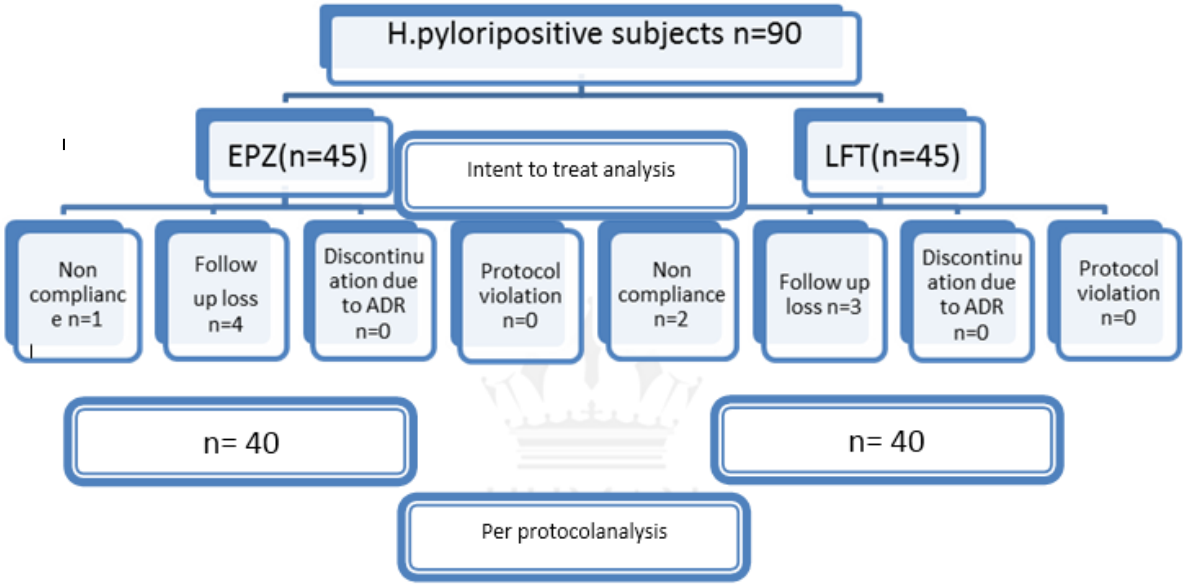

Figure 1. Study Flow and Overall Compliance of Patients during the Study Period

Demographic evaluation:

Age wise prevalence of APD:

Table 1 Age wise prevalence of APD in patients at Gastro care clinic and endoscopy centre in Rajkot

Age group	No. of patient [90]	% patient
15-35	29	32.22
36-55	33	36.66
56-75	24	26.66
76-95	4	4.44

Data is represented as %. Statically analysis is done by willcoxon matched pair test.

*P value<0.05; Statically Significant

P-value >0.05; statistically not significant

APD was found to be more prevalent in the age group of 36-55 years followed by a younger age group of 15-35 years [Table 1]. It is reported that youngsters APD is more common may be due to an increase in stress life and also due to the consumption of more spicy and junk food as found in this study [Susser 2002]. In our study we observed APD are more common in the youngsters and further its prevalence increases in adults who had a higher incidence rate in childhood.

Gender wise prevalence of APD:

The study by [vakiland and mulekar. 1965] has reported that the prevalence of H. pylori-related APD is more common in men because of two reasons. Firstly it could be environmental factors and secondly due to higher gastric acid secretory status has been reported in men. However our study results are consistent with this study although we found that prevalence is not significant in men [table no. 2].

Table 2: Gender wise prevalence of APD in patients at Gastro care clinic endoscopy center in Rajkot.

Gender	No. of patient [n=90]	% patient
Men	51	56.66
Women	39#	43.33

Data is represented as %. Statically analysis is done by willcoxon matched pair test.

*P value<0.05; Statically Significant

P-value >0.05; statistically not significant

Status wise prevalence of APD:

Poor people or people with low socioeconomic status were found to be more infected [75.55%] as shown in [Table 3].this may be due to consumption of unhygienic food and unsafe drinking water and poor sanitation which leads to increase in chances of acquiring H.pylori infection as found in this study [Chuttani 2007].

Table 3: Status wise prevalence of APD

Status	No. of patient[n=90]	% patient
Rich	22	24.44
Poor	68	75.55
P value	<0.005**	

Data is represented as %. Statically analysis is done by Wilcoxon matched pair test.

*P value<0.05; Statically Significant

P-value >0.05; statistically not significant

CONCLUSION

In effectiveness assessment, comparing the effectiveness of both the EPZ and LFT interventions in the study, we found more improvement in gastritis examination and in symptoms like regurgitation and epigastric pain at night with EPZ group whereas LFT regimen was more effective in all other symptoms assessed. However, both the regimens were equally effective with a non-significant difference between both the groups.

In the *H.pylori* eradication assessment, comparing the eradication rate of both EPZ and LFT groups, we found there was more 83.33% eradication observed in the LFT regimen as compared to EPZ regimen 81.48%, although eradication rate difference between both the group was not significant.

In safety assessment, comparing the acute adverse events with both EPZ and LFT treatments. We found, there was no significant difference between both groups. At the same time, the level of appetite and heartburn had shown significant improvement on the 7th day in the LFT group due to beneficial comparative characteristics of LFT.

Lafutidine regimen was found to be equally effective in eradicating H. pylori with earlier symptomatic relief. So, it should be considered as an alternative for PPI-based triple therapy.

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