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A Comparative Evaluation of Lafutidine and Rabeprazole in the Treatment of Gastritis and Peptic Ulcer: A Double-blind, Randomized Study in Indian Patients

Sanjay Kumar[1], Bhupesh Dewan[2*] and Deepashri Shah[2]

[1]*Global Liver and Gastroenterology Centre, Bhopal, India.*
[2]*Medical Department, Zuventus Healthcare Ltd., Mumbai, India.*

Authors' contributions

This work was carried out in collaboration between all authors. Author SK was responsible for clinical examination of the patients, performance of endoscopy, data collection, data interpretation and critical revision of manuscript. Author BD designed the study, performed the statistical analysis, reviewed the protocol, and wrote the manuscript for publication. Author DS was responsible for monitoring the study, data collection, literature search, and compilation of study results. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: To assess the efficacy of lafutidine therapy versus rabeprazole in Indian patients with endoscopically and histologically proven gastritis and peptic ulcer.
Study Design: A double blind, double dummy, randomized, comparative study.
Place and Duration of Study: Global Liver and Gastroenterology Centre, Bhopal, India, between March 2010 and October 2010.
Methodology: A total of 100 patients were enrolled, including 50 with endoscopically and histologically proven gastritis and other 50 with peptic ulcer (over 5 mm in diameter). Each group was randomized to receive either lafutidine or rabeprazole tablet and their corresponding competitor placebo dummy tablet, for a period of 4 weeks. Cure rate was confirmed endoscopically at the end of week 4 as compared to the baseline evaluation. Symptom response and *Helicobacter pylori (H. Pylori)* eradication were also compared among the two drugs at the end of the treatment period.
Results: Complete cure of gastritis was observed in all the patients (100%) treated with

**Corresponding author: Email: bhupesh.dewan@zuventus.com;*

lafutidine and 95.24% [20/21; 95% CI: 76.18 to 99.88%] patients treated with rabeprazole. Complete cure of ulcer was observed in 72.0 (18/25, 95% CI = 50.61 to 87.93%) and 79.16% (19/24, 95% CI = 57.85 to 92.87%) patients treated with lafutidine and rabeprazole respectively. There was no significant difference in gastritis/ulcer cure rate and symptom response rate between the two treatment groups at the end of the study. *H pylori* eradication rates was 82.61% (19/23) in lafutidine group vs 47.37% (9 /19) in rabeprazole group (Δ=35.2%, 95% CI = 3.2 to 67.3%; P= .023). Both, lafutidine and rabeprazole were well tolerated during the entire study.

Conclusion: Endoscopically proven cure rate in patients suffering from gastritis and peptic ulcers is found to be comparable after 4 weeks treatment with Lafutidine and rabeprazole, but lafutidine showed better *H. pylori* eradication rate as compared to rabeprazole.

Keywords: Gastritis; ulcer; lafutidine; rabeprazole; H pylori.

1. INTRODUCTION

Peptic ulcer disease (PUD) and chronic gastritis are most common disorders throughout the world and alleviation of their symptoms is an important goal of treatment [1]. *Helicobacter pylori (H pylori)* is known to play a major role in the development of chronic gastritis, peptic ulcers, and gastric malignancies. Eradication of *H. pylori* infection facilitates ulcer healing and prevents recurrence [2,3].

In the past 30 years, acid suppression therapy has revolutionized the treatment of gastric acid related disorders including GERD and peptic ulcer [4]. The introduction of histamine H_2 receptor antagonists and proton pump inhibitors (PPI) has been associated with a marked improvement in the rate of gastric ulcer healing. However, the high relapse rate following treatment cessation with these drugs has led to the examination of the quality of ulcer healing (QOUH) for gastric ulcers, moreover a reduction in gastric mucosal defense factors is now recognized as one of the possible factors responsible for poor QOUH. Potentiation of gastric mucosal defense factors is important for improving the QOUH and reducing the incidence of relapse of gastric ulcers [5].

Lafutidine, a second generation H_2-receptor antagonist (H_2-RA) used in clinical practice, has been reported to be more potent than first generation H_2-RAs. It has been classified as a second generation H_2-RA because it has long lasting H_2-receptor blocking activity and unlike famotidine and cimetidine, it suppresses acid secretion both during daytime as well as night time [2,3]. After oral administration, lafutidine produces a more rapid rise in intragastric pH than rabeprazole 20 mg in fasting and postprandial *H. pylori* negative patients, resulting in the early resolution of symptoms [6].

In addition to its antisecretory activity, Lafutidine has gastroprotective actions as it strengthens the mucus barrier of the human gastric mucosa [7] and enhances mucosal blood flow via capsaicin-sensitive sensory neurons [3]. Published studies have demonstrated the gastroprotective effects of lafutidine against non-steriodal anti-inflammatory drugs and high endoscopic healing rate in patients with mild reflux oesophagitis, gastritis and peptic ulcer [5,8,9,10,11].

The present double-blind, double dummy, active control, randomized study was undertaken to examine and compare the efficacy and safety of lafutidine and rabeprazole, a widely

prescribed PPI in India for patients with gastritis and peptic ulcer. The secondary objective of the study was to compare the *H. pylori* eradication rate with lafutidine and rabeprazole.

2. MATERIALS AND METHODS

This was a comparative, prospective, double-blind, double dummy, active controlled, randomized study conducted at "Global Liver and Gastroenterology Centre", Bhopal, India. The study protocol was approved by an Independent Ethics committee and the study was conducted under the ethical norms laid down by the Indian Council of Medical Research (ICMR), New Delhi, India, 2004 as well as the ICH-GCP guidelines and the Declaration of Helsinki. It has been registered with the Clinical Trial Registry of India [Registration no: CTRI/2010/091/001057]. A total of 100 patients were enrolled between March 2010 and October 2010, including 50 with endoscopically and histologically proven gastritis and other 50 with peptic ulcer (over 5 mm in diameter), based upon the clinical and endoscopic examination. Presence of *H. pylori* was determined using "biopsy of gastric mucosa taken during endoscopy and rapid urease test performed on the biopsy material". All patients gave informed consent prior to their inclusion in the study. Exclusion criteria included pregnant or lactating patients, presence of perforation or pyloric stenosis, esophageal stricture or intestinal obstruction, previous history of gastrointestinal disease (inflammatory bowel disease, malabsorption syndromes, gastrointestinal malignancy), recent gastrointestinal surgery i.e. within 30 days (vagotomy, Barrett's esophagus and scleroderma), prior administration of PPIs, H_2RAs, NSAIDs, prokinetic agents or any other gastroprotective agent within 7 days of screening and a known history of hypersensitivity to study medications. Drugs like warfarin, theophylline, phenytoin, bisphosphonates, methotrexate, ketoconazole, fluconazole, itraconazole, diazepam, aminopyrine and antipyrine were not permitted at any time during the study.

Study medications comprised of 10 mg lafutidine tablet and 20 mg rabeprazole tablet and their identically matched placebos (dummies). The dosage of lafutidine in gastritis was 10 mg once daily and in peptic ulcer, 20 mg daily (given as 10 mg twice daily) as per the prescribing information. The dosage for rabeprazole was 20 mg once daily in gastritis as well as in ulcer group. Using a computer generated randomization sequence; patients in each group (gastritis and ulcer) were randomized to receive either lafutidine or rabeprazole and their respective dummies. During the 4 weeks of therapy, clinical examinations and laboratory assessments were performed at baseline, week 2 and week 4. Endoscopic examination was performed at baseline and at week 4.

The visual analog scale (VAS), a scoring system from 0 (lack of symptom) to 100 (high severity) [12], was used to score the severity of the seven subjective clinical symptoms (Abdominal Pain, Bloating, Belching, Nausea, Vomiting, Loss of Appetite and Heartburn) at baseline and at each follow up visit. The topography and severity of endoscopic gastritis was classified according to the "Sydney System of Endoscopic Classification" [13,14]. Based on the endoscopy, the topography of gastritis was noted as antrum gastritis, corpus gastritis or both (pangastritis).

Peptic ulcer stage was classified using a 6-stage system "Sakita-Miwa classification": classified as Active (A1: Ulcer that contains mucus coating, with marginal elevation because of edema, A2: Mucus-coated ulcer with discrete margin and less edema than active stage A1), Healing (H1: Unhealed ulcer covered by regenerating epithelium < 50%, with or without converging folds, H2: Ulcer with a mucosal break but almost covered with regenerating epithelium), and Scarring (S1: Red scar with rough epithelialization without mucosal break,

S2: White scar with complete re-epithelialization) [11]. The size of the ulcer was defined as the longitudinal diameter of the gastric/ duodenal ulcer. Ulcer healing was assessed by measuring the changes in ulcer size and stage.

The "overall treatment evaluation" (OTE) assessed the Patient's Perspective on Symptom relief on a 6-point Likert scale [1: "The treatment made me a lot worse"; 2: "The treatment made me slightly worse"; 3: "The treatment made no change to my symptoms"; 4: "The treatment made me slightly better"; 5: "The treatment made me a lot better"; 6: "The treatment completely relieved my symptoms"]. Adverse events, if any, were reported during the follow up visits.

Outcome measures included the cure rate of gastritis or ulcer, symptom relief, ulcer size reduction, presence of redness, oozing, edema and overall treatment evaluation. Cure Rate was defined as absence of gastritis or ulcer, confirmed by endoscopy, after 4 weeks of treatment.

The changes in severity of individual symptoms between the visits in each treatment group were compared by "Wilcoxon Rank Sum" Test. A comparative evaluation for the mean score reduction between the two groups was performed by "Mann-Whitney U-test". The proportions of patients were reported as "percentage" along with their "95% confidence interval" (CI) and the comparison between the treatment groups were performed using Fisher's exact test. All data are presented as mean ± standard deviation (S.D) unless stated otherwise. *P* value less than.05 was considered significant.

3. RESULTS

The study comprised of two groups: patients with gastritis and patients with peptic ulcer. A total of 100 patients, 50 in each group were enrolled. Thus in each treatment group (lafutidine and rabeprazole), there were 50 patients (25 with gastritis and 25 with peptic ulcer). Of the 50 patients who received rabeprazole, five patients, one with peptic ulcer and four with gastritis were lost to follow-up. All patients receiving lafutidine completed the study as per the protocol.

3.1 Patient Profile

The enrolled patients comprised 77 men and 18 women, with a mean age of 40.35 ± 12.17 years (range: 19–79). Baseline characteristics of the study population are listed in Table 1. The two treatment groups were well matched for gender, age, body weight and other baseline diagnosis.

3.2 Symptom Response Rate

The proportion of patients reporting clinical symptoms like abdominal pain, bloating, belching, nausea, vomiting, loss of appetite and heartburn at baseline (Table 1) and after 2 and 4 weeks of therapy is shown Fig. 1. None of the patients in lafutidine or rabeprazole group reported nausea or loss of appetite in the subsequent follow-up visits. When the symptom response was evaluated, the proportion of patients in both the groups reported resolution from the symptoms and there was no significant difference between lafutidine and rabeprazole group after 4 weeks of treatment.

Table 1. Baseline demographic & clinical characteristics of study population

	Lafutidine [n= 50]	Rabeprazole [n= 45]
Sex, n (%)		
Male	42 (84.0)	35 (77.77)
Female	8 (16.0)	10 (22.22)
Age (yrs), mean ± SD	39.90 ± 12.25	40.84 ± 12.19
Body mass index (kg/m^2), mean ± SD	21.78 ± 3.38	21.38 ± 4.00
Positive *H. Pylori*, n (%)	23 (46.0)	19 (42.22)
Endoscopic findings, n (%)		
Gastritis	25 (50.0)	21 (46.66)
Antrum	20 (80.0)	14 (66.66)
Corpus	5 (20.0)	7 (33.33)
Peptic ulcer	25 (50.0)	24 (53.33)
Gastric	1 (4.0)	0 (0.0)
Duodenal	24 (96.0)	24 (100.0)
Oozing	11 (22.0)	4 (8.88)
Redness	29 (58.0)	24 (53.33)
Edema	10 (20)	12 (26.66)
Gastritis clinical symptoms (n, %)		
Abdominal Pain	44 (88)	38 (84.4)
Bloating	17 (34)	19 (42.2)
Belching	9 (18)	11 (24.4)
Nausea	3 (6)	3 (6.7)
Vomiting	13 (26)	10 (22.2)
Loss of appetite	1 (2)	2 (4.4)
Heartburn	20 (40)	16 (35.6)

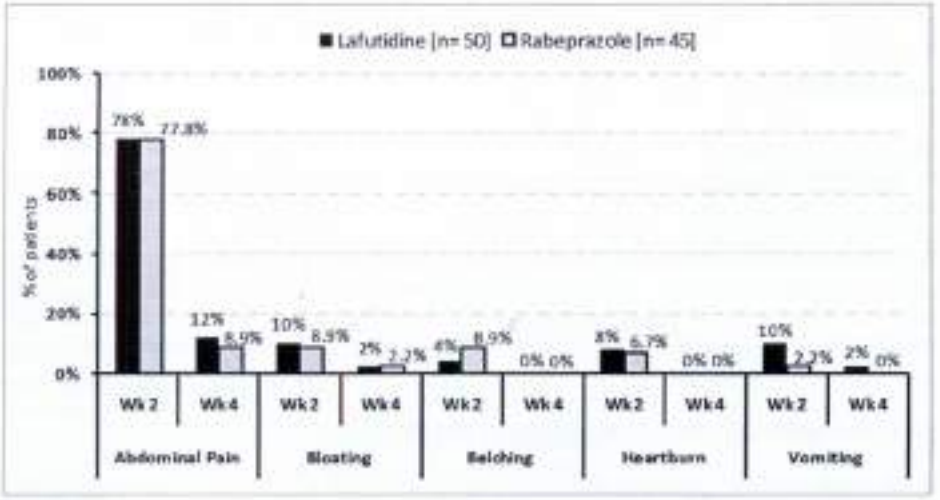

Fig. 1. Proportion of patients with clinical symptoms after 2 and 4 weeks (Wk) of therapy

There was a significant reduction in the VAS score from the baseline in both groups (Table 2). A sustained relief (a score of 0 on the VAS scale) was observed in all the patients, receiving either of the drugs in symptoms of belching and heartburn, at the end of 4 weeks. No significant difference in symptom relief for any clinical symptom was observed between the two groups.

Table 2. Change in VAS Sore (mean ± S.D) for clinical symptoms reported at baseline

Clinical Symptom	Baseline	Week 2	Week 4
Abdominal Pain			
Lafutidine [n= 44]	63.4 ± 16.8	39.3 ± 18.4*	5.9 ± 15.7*
Rabeprazole [n= 38]	65.8 ± 15.2	41.8 ± 18.9*	3.9 ± 12.4*
P value #	.54	.57	.78
Bloating			
Lafutidine [n= 17]	44.1 ± 15.0	7.6 ± 13.0*	1.2 ± 4.9*
Rabeprazole [n= 19]	47.4 ± 15.2	5.3 ± 10.7*	2.1 ± 9.2*
P value #	.61	.68	1.0
Belching			
Lafutidine [n= 9]	42.2 ± 10.9	4.4 ± 8.8*	0.0 ± 0.0*
Rabeprazole [n= 11]	40.9 ± 14.5	10.9 ± 16.4*	0.0 ± 0.0*
P value #	.81	.51	.96
Heartburn			
Lafutidine [n=20]	43.5 ± 20.1	6.0 ± 13.1*	0.0 ± 0.0*
Rabeprazole [n= 16]	40.0 ± 13.2	6.3 ± 13.6*	0.0 ± 0.0*
P value #	.89	.98	.98
Vomiting			
Lafutidine [n= 13]	30.0 ± 15.3	10.8 ± 15.5*	3.1 ± 11.1*
Rabeprazole [n= 10]	33.0 ± 21.6	2.0 ± 6.3*	0.0 ± 0.0*
P value #	.64	.23	.78

**P < .001 vs. baseline, within the group. # P-value between the two treatment groups.*

3.3 Observations upon Endoscopy

There was reduction in the proportion of patients having redness, edema and oozing in both the treatment groups after 4 weeks of therapy. At the end of the study, 6.00 (3/50, 95% CI= 1.25 - 16.55%) and 2.22% (1/45, 95% CI= 0.06 - 11.77%) of patients had redness (*P*=.25), 2.0 (1/50, 95% CI= 0.05- 10.65%,) and 2.22% (1/45, 95% CI= 0.06 - 11.77%) had oozing (*P*= .47) in lafutidine and rabeprazole group respectively. In addition edema was reported in 6.0% (3/50, 95% CI= 1.25 - 16.55%) of lafutidine treated group and, 2.22% (1/45, 95% CI= 0.06 - 11.77%) with rabeprazole group (*P*= .29) at the end of 4 weeks. Both, lafutidine and rabeprazole groups had no significant difference in the results obtained after endoscopic observations.

3.3.1 Resolution of signs of endoscopic gastritis

At baseline, erosive gastritis was observed in two patients in each treatment group. The remaining patients were diagnosed as non-erosive gastritis upon endoscopy. After 4 weeks of therapy, complete endoscopic healing was observed in all the patients receiving lafutidine while one patient (4.76%) in rabeprazole group, diagnosed with antrum gastritis, persisted

with signs of gastritis. There was no statistically significant difference (P= .4) between the two treatment groups in the patients achieving complete cure from gastritis. (Fig. 2).

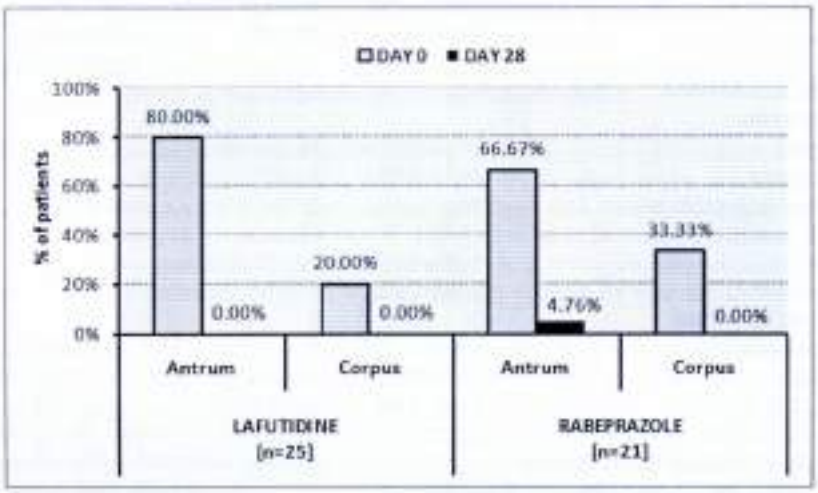

Fig. 2. Proportion of patients with gastritis before and after therapy upon endoscopic examination

3.3.2 Resolution of Signs of Endoscopic Peptic Ulcer

After 4 weeks of therapy, 72.00 (18/25, 95% CI = 50.61 to 87.93%) and 79.16% (19/24, 95% CI = 57.85 to 92.87%) of the patients showed no signs of gastric or duodenal ulcer upon endoscopy in lafutidine and rabeprazole group respectively. No significant difference was observed in the cure rates of ulcer based on ulcer stage among the two groups (Table 3). The proportion of patients with complete cure from gastric or duodenal ulcer corresponded with a reduction in the ulcer size as well (Table 4).

Table 3. Cure rate of ulcer based on the ulcer stage after 4 weeks of therapy

Ulcer Stage	Lafutidine [n=25]	Rabeprazole [n=24]	*P*-value (Between treatment groups)
A1 stage at baseline	14	17	$P = 1.0$
After 4 weeks			
Cured	12 (85.71%)	15 (88.23%)	
Not cured	2 (14.28%)	2 (11.76%)	
A2 stage at baseline	10	5	$P = 1.0$
After 4 weeks			
Cured	6 (60.0%)	3 (60.0%)	
Not cured	4 (40.0%)	2 (40.0%)	
H1 stage at baseline	1	2	$P = 1.0$
After 4 weeks			
Cured	0 (0.0%)	1 (50.0%)	
Not cured	1 (100.0%)	1 (50.0%)	

The present study comparing lafutidine, a second generation H_2-RA antagonist with rabeprazole, has demonstrated that both lafutidine and rabeprazole are equally effective in the treatment of gastritis and ulcer. The results of this study are consistent with a previous study [11], wherein lafutidine was compared to rabeprazole in post-ESD (endoscopic submucosal dissection) gastric ulcers. In another study [3], ulcer cure rate and symptom response rate were similar in the lafutidine and lansoprazole group.

Lafutidine, in addition to its antisecretory activity, possess gastro protective action which includes increase in mucin biosynthesis via stimulation of nitric oxide production [16,17], increasing the thickness of the surface mucus gel layer and maintaining gastric mucosal blood flow and bicarbonate response [7,18]. Lafutidine has been proposed to inhibit the secretion of IL-8 in the gastric mucosa, thereby preventing mucosal inflammation [20]. It also inhibits the neutrophil activation which reduces damage caused by free radicals [21].

H. pylori is known to play a major role in the development of chronic gastritis, peptic ulcers, and gastric malignancies [3] and its eradication facilitates ulcer healing and prevents recurrence [2]. In a preclinical study it was demonstrated that lafutidine inhibited the adherence of *H. pylori* to the cells and subsequent IL-8 release, indicating a novel mechanism by which lafutidine protects against the mucosal inflammation associated with *H. pylori* infection [20]. Previously published studies have demonstrated that lafutidine is as effective as PPIs for the eradication of *H. pylori* but unlike lansoprazole the activity of lafutidine was not affected by CYP2C19 genotype. [2,3,19]. In the present study, it was also observed that a higher proportion of patients in lafutidine group became *H. pylori* negative at the end of 4 weeks therapy in comparison to those in rabeprazole group.

Anti-ulcer activity of lafutidine had been studied previously in animals using rats. It prevented the indomethacin-induced antral ulcer formation and accelerated healing by reducing the area of ulcer in a dose-dependent manner [22]. Evidences show that lafutidine can also improve the quality of gastric ulcer healing in humans. The gastric ulcer healing rate was 92.1% in the lafutidine group and in patients with large ulcers (10 mm or more), lafutidine showed better healing than famotidine [5]. Furthermore, effectiveness of lafutidine against NSAIDs-induced ulcer was also reported to be high as it reduces the ulcer relapse after discontinuation of the treatment [8,23].

Lafutidine, unlike cimetidine and famotidine, accelerates the healing of mucosal injuries in ammonia- and TCA-induced chronic gastritis models [24]. In patients having gastritis, lafutidine has been reported to reduce inflammation not only by inhibiting acid secretion but also by strengthening the mucus barrier of the human gastric mucosa [7].The current study also showed that lafutidine was effective in curing gastritis and ulcer based on the endoscopy performed at the beginning and end of the study.

Overall, lafutidine and rabeprazole were well tolerated and no adverse events were reported by patients in either treatment groups. The current study has its limitation in terms of smaller sample size and subjective interpretation of VAS scale as it represents "patient-weighted assessment" of symptoms but it was supported with endoscopy, histology and *H. pylori* analysis. Further trials are suggested to confirm the superiority of Lafutidine over rabeprazole in the management of gastritis and peptic ulcer.

5. CONCLUSION

Endoscopically proven cure rate in patients suffering from gastritis and peptic ulcers is found to be comparable after 4 weeks treatment with Lafutidine and rabeprazole, but lafutidine shows better *H. pylori* eradication rate as compared to rabeprazole.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that the trial has been examined and approved by the Jagruti Independent Ethics Committee and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Dr. Sanjay Kumar has no financial relationships with Zuventus Healthcare Ltd that might have an interest in the submitted work and no other relationships or activities that could appear to have influenced the submitted work.

Dr. Bhupesh Dewan and Ms. Deepashri Shah are employees of Zuventus Healthcare Ltd.

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