e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(7); 203-212

Original Research Article

A Randomized Comparative Study of Levofloxacin Based Triple Therapy with Standard Triple Therapy for Helicobacter Pylori Eradication

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Received: 29-03-2023 / Revised: 281-04-2023 / Accepted: 30-05-2023

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Conflict of interest: Nil

Abstract:

Background: The isolation of Helicobacter pylori has opened the floodgates to a new era of discovery and understanding of gastro-duodenal pathology and heralded a revolution in the thinking about the pathophysiology and the treatment of PUD in particular. Preliminary data on triple therapies including either levofloxacin or azithromycin have shown positive results and suggest that these compounds could be promising for Helicobacter pylori treatment. As more is learnt about the organism and the disease process, it is hoped that a simple and an effective cure will be discovered.

Aim: Comparison of levofloxacin-based triple therapy with standard triple therapy for helicobacter pylori eradication

Methods and Materials: The study was conducted in 72 patients attending the OPD of Gastroenterology. Patients were randomized according to a computer-generated randomization schedule, to receive a 7 days treatment with either Esomeprazole 20mg, Levofloxacin 500mg and Azithromycin 500mg, once daily (ELA) or Esomeprazole 20mg, Clarithromycin 500mg and Amoxicillin 1g twice daily (ECA). Esomeprazole was given 30 minutes prior to breakfast and dinner, whilst the antibiotics were taken together immediately after meals. The use of alcohol was discouraged during the study period. All the patients were continued with esomeprazole 20mg once daily for the next 3 weeks, followed by a drug-free period of 1 week. Within a week following completion of the 7 days study medications, patients came for the end-of-treatment assessment.

Results: Twenty-nine (85.3%) patients in the ELA group, 33(94.3%) patients in the ECA group experienced an improvement in the severity of the symptoms, whereas 5(14.7%) patients in the ELA group and 2(5.7%) patients in the ECA group felt that the symptoms were unresolved or even worsened. In the ELA group, the lesions were completely healed in 21(61.76%) cases as compared to 27(77.1%) cases in the ECA group (X^2=2.32, p=0.127). Helicobacter pylori infection was eradicated in 23(67.6%) cases, in the ELA group, whereas the eradication rate with the ECA group was 77.1% (27 cases) (X^2=0.779, p=0.377).

Conclusion: The present study demonstrates that once daily levofloxacin plus azithromycin-based triple therapy achieves Helicobacter pylori eradication rate comparable to that of the standard, twice daily triple therapy. Patient compliance, drug tolerability and side effects profile were almost the same in the two treatment groups. Hence levofloxacin-based triple therapies may represent a promising, alternative therapeutic option in the first-line therapy for Helicobacter pylori infection

Keywords: Levofloxacin based triple therapy, standard triple therapy, helicobacter pylori eradication.

Introduction

Peptic Ulcer Disease (PUD) is one of the most common medical and surgical problems encountered worldwide. It has been considered to be a 'disease of civilization'. It is defined pathologically as the disruption in selective areas of gastrointestinal mucosa, where there is an evidence of increased acid peptic digestion. PUD is believed to be the single end point of a group of heterogeneous disorders, which include abnormal secretion rates of gastric acid and bicarbonate. Other factors like stress, diet, drugs, hormones and genetic predisposition are thought

to play a contributing role in the etiopathogenesis of PUD. For many decades the dictum 'No acid, No ulcer' dominated thinking on the pathogenesis of peptic ulcer. Since the isolation of Helicobacter pylori, by Dr. Robin Warren and Dr. Barry Marshall (1983)1 in Perth, Western Australia, the study of gastric bacteriology has gained significant impetus. The isolation of Helicobacter pylori has opened the floodgates to a new era of discovery and understanding of gastro-duodenal pathology and heralded a revolution in the thinking about the path physiology and the treatment of PUD in particular.

Presently, a causal relationship between Helicobacter pylori and PUD has been established[2]. Improvements in diagnostic and therapeutic options, combined with the gradual acceptance of the etiological role of an infective agent in peptic disease have led to a remarkable change in the management of gastro-duodenal conditions in the past decade. Antibacterial therapy can change the natural history of PUD. The eradication of Helicobacter pylori significantly reduces the relapse of peptic ulcers[3].

Many drug regimens have been proposed for Helicobacter pylori eradication. The recommended standard eradication therapy is based on a twice daily intake of a Proton Pump Inhibitor (PPI) or Ranitidine Bismuth Citrate (RBC) along with two antibiotics among clarithromycin, amoxicillin and imidazoles for 1-2 weeks, with an eradication rate that is generally 85 – 90%[4]. Low cure rates of eradication therapies have been reported due to antibiotic resistant strains and poor patient compliance. The use of simpler dosing schedules and antibiotics, towards which bacterial resistance has not been developed could increase the effectiveness of eradication therapy. Preliminary data on triple therapies including either levofloxacin or azithromycin have shown positive results and suggest that these compounds could be promising for Helicobacter pylori treatment[5]. As more is learnt about the organism and the disease process, it is hoped that a simple and an effective cure will be discovered. This study was carried out to compare two regimens in the eradication of Helicobacterpylori. These regimens were:- Once daily esomeprazole, levofloxacin and azithromycin triple and The standard (clarithromycin, amoxicillin and esomeprazole), twice daily triple therapy

Source of Data:

The study was conducted in 72 patients attending the OPD of Gastroenterology, MS Ramaiah Medical College Teaching Hospital and Memorial Hospital, Bangalore. The study was conducted for a period of one year, Nov 2005 – Oct 2006.

Method of collection of Data:

Patients attending the Gastroenterology OPD, with symptoms of acid peptic disease were considered for this study.

Inclusion criteria:

- Patients of either sex.
- Patients aged 18-60yrs.
- Patients with acid peptic disease (non-ulcer dyspepsia, gastro-duodenal ulcers and erosions).

Exclusion criteria:

- Patients on NSAIDs, anticoagulants, antibiotics or corticosteroids, in the past 30 days.
- Patients with co-morbid conditions – IHD, congestive cardiac failure, renal failure.
- Pregnant and lactating women.
- Patients with features of portal hypertension, gastric orany
- other malignancy or evidence of significant gastrointestinal bleed.
- Patients with known allergy to medications used.
- Patients with previous gastric or esophageal surgery.

Sample size calculation:

Numeric Results of Tests Based on the Difference: P1 - P2

H0: P1-P2=0. H1: P1-P2=D1<>0. Test Statistic: Z test with pooled variance.

The formula used

Z 21□ □(P (1 □P) □P (1 □P)

n□ 2 1 1 2 2

d 2

Where P1 and P2 are anticipated proportions d=absolute precession, Confidence level=0.05

Group sample sizes of 36 in group one and 36 in group two achieve 90% power to detect a difference between the group proportions of -0.0600.

The proportion in group one (the treatment group) was assumed to be 0.7600 under the null hypothesis and 0.7000 under the alternative hypothesis. The proportion in group two (the control group) is 0.7600. The statistical test used was the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.0500.

Study procedure:

Informed consent was obtained after fully explaining the procedure and the consequences, in patients' own language (Annexure-1)

The work up included a detail history taking as per the proforma (Annexure-2), symptom analysis and clinical findings. History of habits, family history and drug history were taken as they have a direct bearing on PUD.

Endoscopy procedure and Helicobacter pylori assessment:

After an overnight fast, all patients underwent upper GI endoscopy, using EG-2940 (Japan) Pentax video-endoscope (Annexure-4). Endoscopy was done by a qualified gastroenterologist. Mucosal specimens were obtained from each of the patients, from the antrum and the gastric body for the detection of Helicobacter pylori, using biopsy forceps (Annexure 4).

Helicobacter pylori infection at the time of entry was determined by RUT and histological assessment (Annexure 4). RUT was used for the detection of Helicobacter pylori infection, because of its cost effectiveness, ease with which it can be performed, quick results and high sensitivity/specificity rates.

Two biopsy specimens, one each from the antrum and corpus were placed in 2% Christensen's urea solution which contained phenol red as the pH indicator. A colour change to pink within half an hour was taken as a positive RUT and indicated by the presence of Helicobacter pylori. The histological assessment of Helicobacter pylori status was performed using biopsy specimens stained with Giemsa.

Patients were considered to be positive for Helicobacter pylori only when both the rapid urease test and the histological examination showed positive results for Helicobacter pylori. Patients initially classified as positive for Helicobacter pylori on the basis of the RUT were reclassified as negative if the histology report came negative for the same.

Study design:

Helicobacter pylori positive patients were classified to peptic ulcer disease (PUD) group, non-ulcer dyspepsia (NUD) group or the gastro-esophageal reflux disease (GERD) group, based on the predominant symptoms and endoscopy findings. They were included in the GERD group when heartburn or acid regurgitation were the predominant symptoms and no ulcer was found in the stomach or duodenum, otherwise they were included in the PUD group.

Patients were randomized according to a computer generated randomization schedule, to receive a 7 days treatment with either Esomeprazole 20mg, Levofloxacin 500mg and Azithromycin 500mg, once daily (ELA) or Esomeprazole 20mg, Clarithromycin 500mg and Amoxicillin 1g twice daily (ECA).

Esomeprazole was given 30 minutes prior to breakfast and dinner, whilst the antibiotics were taken together immediately after meals. The use of alcohol was discouraged during the study period. All the patients were continued with esomeprazole 20mg once daily for the next 3 weeks, followed by a drug free period of 1 week.

Follow up - 1: Within a week following completion of the 7 days study medications, patients came for the end-of-treatment assessment.

Treatment compliance was estimated by using a scale83.

Excellent – Drug taken for 7days

Good - Drug taken for 5-6days

Poor – Drug taken for <5days

Incidence of side effects was checked using a standardized questionnaire84 (Annexure-3), given to the patient at the time of enrollment and to be filled in during the treatment period, indicating the type and degree of interference with daily activity of the patient as follows:

- No side effects
- Slight discomfort, not interfering with daily activity
- Moderate side effects, sometimes interfering with daily activity
- Severe side effects, work not possible
- Side effects severe enough to discontinue treatment
- Tolerability was analyzed in all compliant patients based on the side effects grading. The patients assigning themselves to Groups A or B were considered to have tolerated the treatment well, while assignment to groups C, D, E indicated poor tolerance.
- Excellent tolerance – Group A Good tolerance – Group B
- Poor tolerance – Groups C, D, E

Follow up – 2: Four to six weeks after the conclusion of therapy, an endoscopy, RUT and biopsy (as at entry) was performed in all patients. Helicobacter pylori eradication was considered to have been achieved when both histological detection and RUT were negative in all gastric sites tested. Ulcer healing was defined as a complete re-epithelialization of the ulcerative lesion at endoscopy.

Clinical response:

Symptoms of abdominal pain, bloating or postprandial fullness, belching, acid reflux and heartburn were assessed.

A pre-treatment symptom was considered to be resolved or improved if the patient felt a notable improvement in the symptoms. A symptom was considered to be unresolved if it stayed the same or evenworsened.

Method of Statistical Analysis:

Data analysis was carried out using Statistical Package for Social Science (SPSS, V 10.5). Chi square test was used for statistical analysis. The "p" value of less than 0.05 was accepted as indicating statistical significance.

Results

A total of 72 Helicobacter pylori positive patients were enrolled into the study. Both the treatment groups matched with respect to age, gender, diet, habits, co-morbid conditions and the type of disease. Male: Female ratio was – 2.4:1 (table1). Majority of the patients, (47 cases – 65%) were in the age group 25 – 55 years.

Age range was 18 – 72 years. (Table 2). The distribution of most common symptoms in both treatment groups was comparable having pain in abdomen as most common symptoms in both categories (80.5% vs 88.8%). It was followed by regurgitation (36% vs 25%). (table3). 38 patients (52.8%) were symptomatic for a duration ranging from 1month – 1 year, followed by 22(30.6%) who had symptoms for 1 – 5 years (X2=5.33, p=0.149)(figure 1). 2 patients (5.9%) in ELA group had poor compliance as compared to 1(2.9%) in the ECA group. (X2=1.335, p=0.721) (Figure 2).

On comparison between two categories for side effects then it was observed that the difference in findings between the two categories was non-significant statistically. (X2=1.41, p=0.703). No side effects (79.40% vs 77.10%).

Slight discomfort not interfering with daily activity. (14.70% vs 17.10%) was the most common side effects. Moderate side effects, sometimes interfering with daily activity. (2.90% vs 5.70%). (Figure 3). Multiple side effects in same patient was found among 23.5% study participants in treatment A group and 22.9% in treatment B group. Taste disturbance was observed in 37.5% in treatment A group and 12.5% in category B. Pain in abdomen (0 vs 25%), diarrhea (25% vs 50%), nausea/vomiting (25% vs 12.5%), skin rash (12.5% vs 0), bloating (0 vs 25%). (table 4).

Excellent tolerance (79.4% vs 77.1%). Good tolerance (14.7%), poor tolerance (5.9% vs 5.7%). The difference in findings was statistically non-significant. (X2=0.076, p=0.963). (table 5) Twenty nine (85.3%) patients in the ELA group, 33(94.3%) patients in the ECA group experienced an improvement in the severity of the symptoms, whereas 5(14.7%) patients in the ELA group and 2(5.7%) patients in the ECA group felt that the symptoms were unresolved or even worsened.(table 6).

In the ELA group, the lesions were completely healed in 21(61.76%) cases as compared to 27(77.1%) cases in the ECA group (X2=2.32, p=0.127). (Figure 4).

Helicobacter pylori infection was eradicated in 23(67.6%) cases, in the ELA group, whereas the eradication rate with the ECA group was 77.1 %(27 cases) (X2=0.779, p=0.377). (Figure 5)

Table 1: Characteristics of the study population

Parameters	Treatment A (ELA)	Treatment B (ECA)	Total	p value
Age	44.3 ± 14.78	46.8±14.50	45.5±14.59	0.471
Sex:				
Male	25(69.4%)	26(72.2%)	51(70.8%)	0.795
Female	11(30.6%)	10(27.8%)	21(29.2%)	
Diet:				
Vegetarian	13(36.1%)	15(41.7%)	28(38.9%)	0.629
Non Vegetarian	23(63.9%)	21(58.3%)	44(61.1%)	
Habits:				
No habits	18(50%)	23(63.9%)	41(56.9%)	
Smoking	4(11.1%)	5(13.9%)	9(12.5%)	0.203
Alcohol	10(27.8%)	3(8.3%)	13(18.1%)	
Both	4(11.1%)	5(13.9%)	9(12.5%)	
Co-morbid Conditions:				
Nil	30(83.3%)	29(80.6%)	59(81.9%)	
Diabetes Hypertension	1(2.8%) 3(8.3%)	1(2.8%) 3(8.3%)	2(2.8%) 6(8.3%)	0.733
Diabetes + Hypertension	1(2.8%)	3(8.3%)	4(5.6%)	
Epilepsy	1(2.8%)	-	1(1.4%)	
Type of disease:				
PUD* NUD**	30(83.3%) 2(5.6%)	26(72.2%) 3(8.3%)	56(77.8%) 5(6.9%)	0.521

GERD***	4(1.1%)	7(19.4%)	11(15.3%)	
Lost to follow-up	2(5.6%)	1(2.8%)	3(4.2%)	-

* Peptic ulcer disease, ** Non ulcer dyspepsia, *** Gastro esophageal reflux disease

Table 2: Age wise distribution of cases

Age	Treatment		Total
	Treatment A (ELA)	Treatment B (ECA)	
15-24 yrs	3(8.3%)	2(5.6%)	5(6.9%)
25-34 yrs	6(16.7%)	5(13.9%)	11(15.3%)
35-44 yrs	10(27.8%)	10(27.8%)	20(27.8%)
45-54 yrs	7(19.4%)	9(25.0%)	16(22.2%)
55-64 yrs	4(11.1%)	3(8.3%)	7(9.7%)
65-74 yrs	6(16.7%)	7(19.4%)	13(18.1%)
Total	36	36	72
X^2=0.761, p=0.979			

Table 3: List of presenting complaints:

Symptoms – Mostcommon [a]	Treatment A (n=36)	Treatment B (n=36)	p value
Pain abdomen	29(80.5%)	32(88.8%)	0.329
Regurgitation	13(36%)	9(25%)	0.309
Nausea	8(22%)	11(30.5%)	0.426
Bloating	4(11%)	6(16.6%)	0.499

[a] Multiple symptoms in the same patient

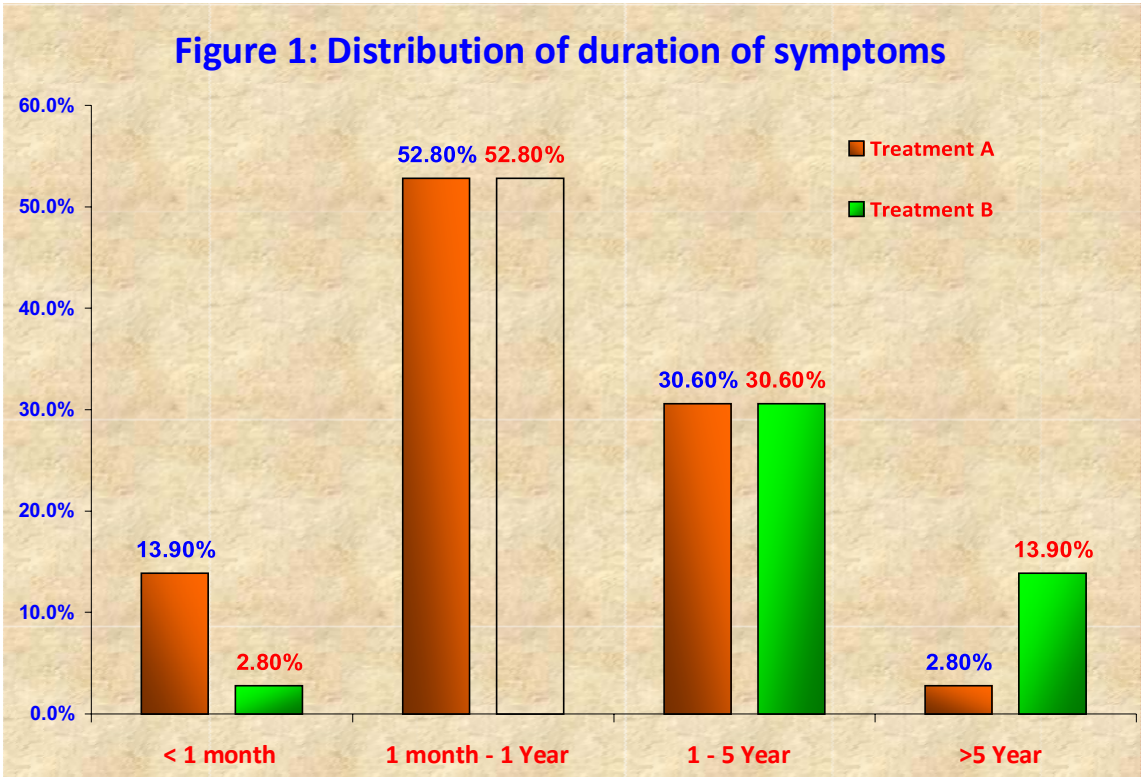

Figure 1: Distribution of duration of symptoms

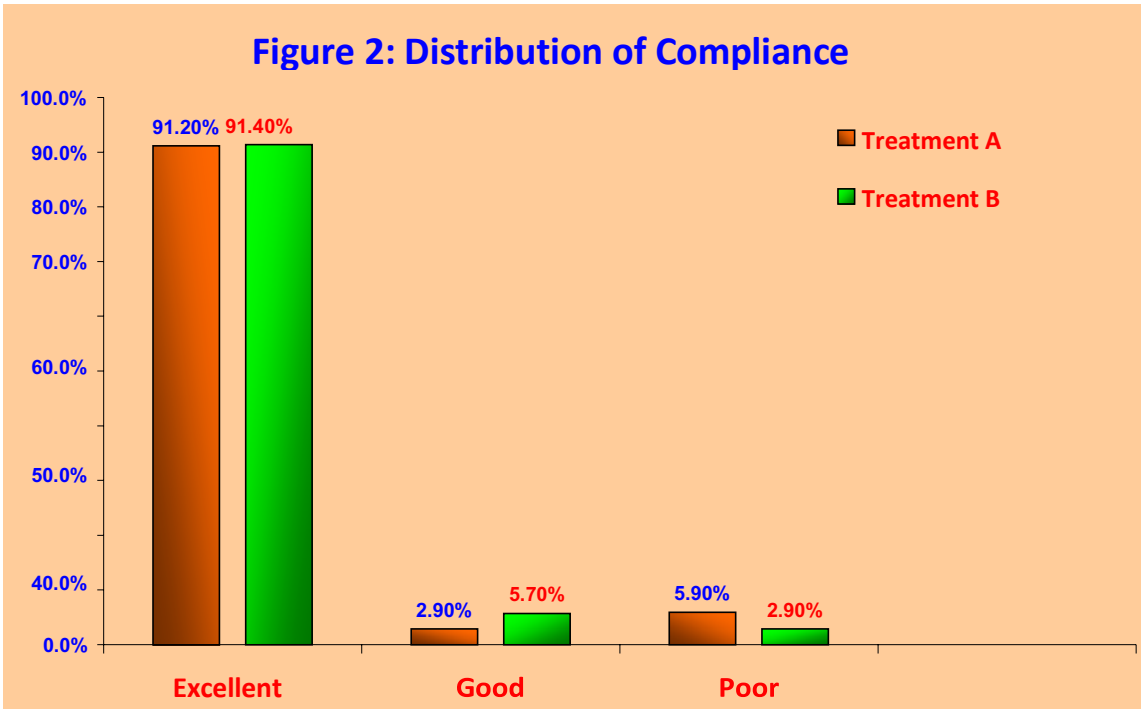

Figure 2: Distribution of Cumpliance

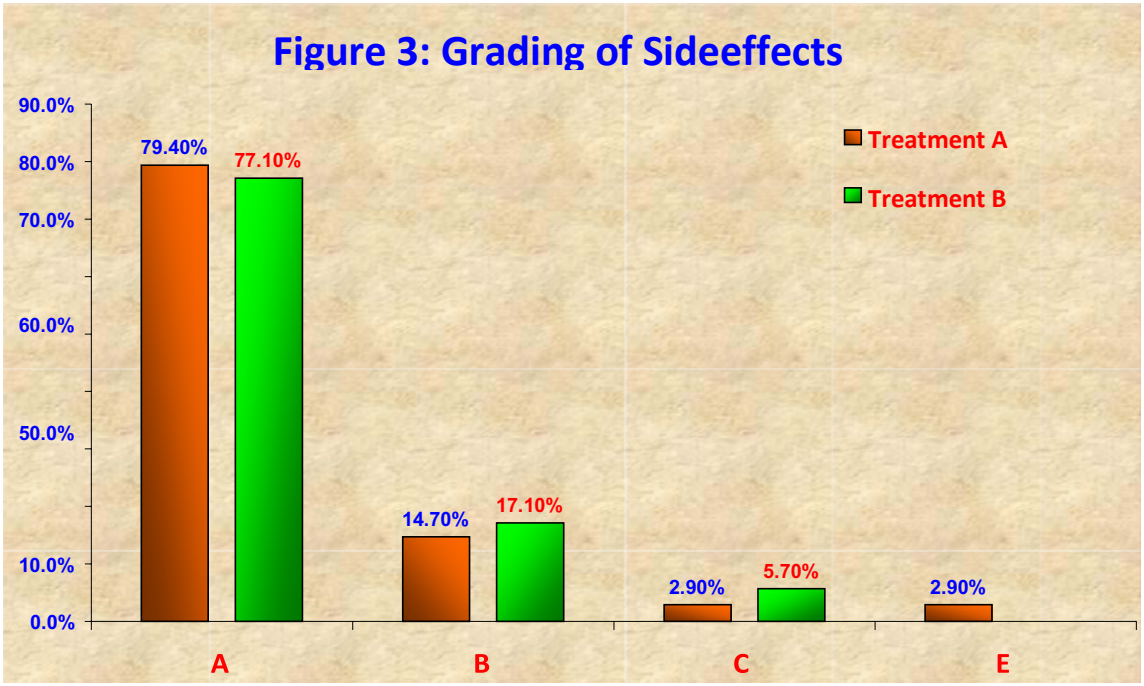

Figure 3: Grading of Sideeffects

Table 4: List of side effects

Side effects	Treatment A ELA (n=34)	Treatment B ECA (n=35)	p value
Incidence – Most common [a]	8(23.5%)	8(22.9%)	0.947
Taste disturbance	3(37.5%)	1(12.5%)	0.569
Pain abdomen	-	2(25%)	-
Diarrhea	2(25%)	4(50%)	0.608
Nausea/Vomiting	2(25%)	1(12.5%)	1.00
Skin rash	1(12.5%)	-	-
Bloating	-	2(25%)	-

[a]Multiple side effects in the same patient

Table 5: Assessment of tolerance:

Tolerance	Treatment		Total
	Treatment A	Treatment B	
Excellent	27(79.4%)	27(77.1%)	54(78.3%)
Good	5(14.7%)	6(17.1%)	11(15.9%)
Poor	2(5.9%)	2(5.7%)	4(5.8%)
Total	34(100%)	35(100%)	69(100%)
X^2=0.076, p=0.963			

Table 6: Distribution of clinical response at the end of the study according to the initial severity of the symptom

Treatment	Symptoms Severity	Clinical Response at the end ofstudy		Total	P value
		Resolved /Improved	Unresolved /Worsened		
Treatment A	Mild	11(84.6%)	2(15.4%)	13	
	Moderate	15(88.2%)	2 (11.8%)	17	
	Severe	3(75%)	1(25%)	4	
	Total	29(85.3%)	5(14.7%)	34(100%)	0.795
Treatment B	Mild	13(100%)	-	13	
	Moderate	17(89.5%)	2(10.5%)	19	
	Severe	3(100%)	-	3	
	Total	33(94.3%)	2(5.7%)	35(100%)	0.409

Treatment	Chi-Square Value	df	'p' value
Treatment A	0.460	2	0.795
Treatment B	1.786	2	0.409

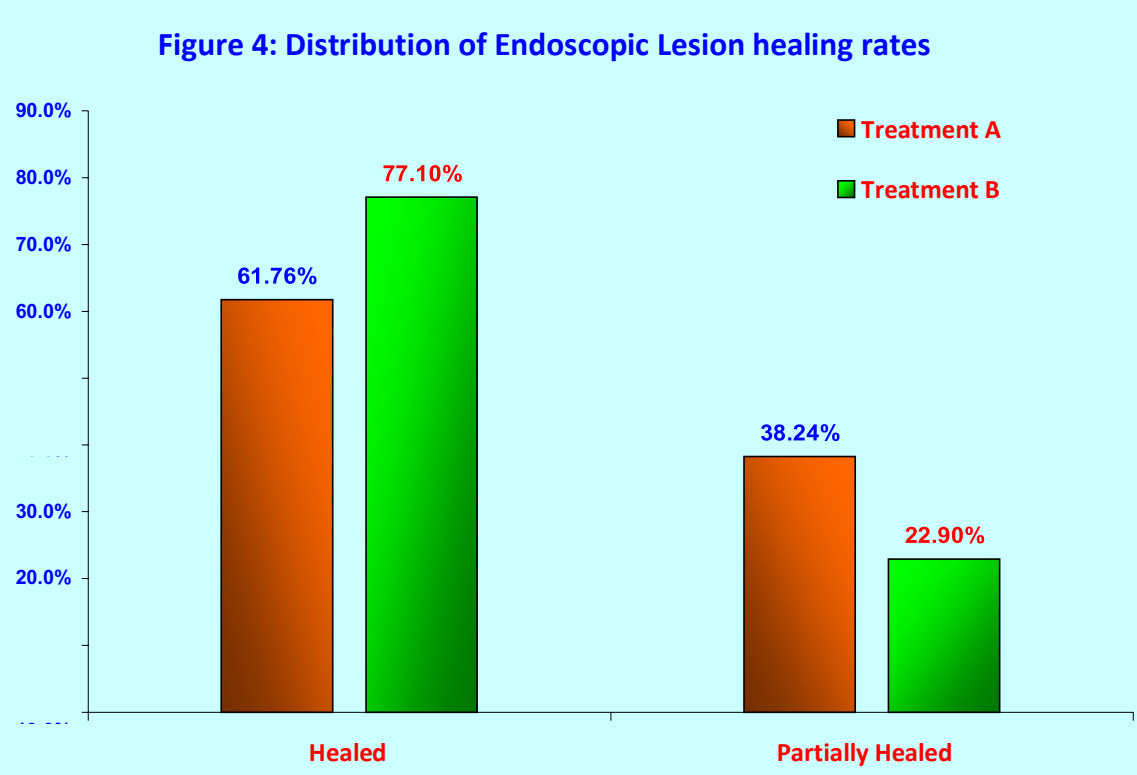

Figure 4: Distribution of Endoscopic Lesion healing rates

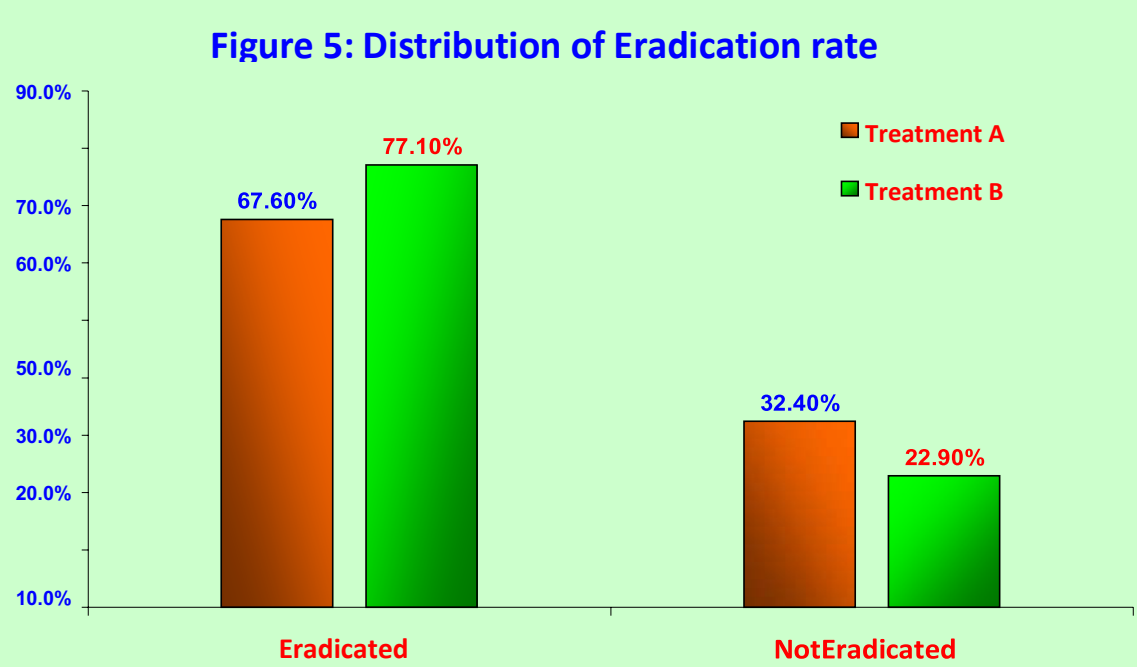

Figure 5: Distribution of Eradication rate

Discussion

The role of Helicobacter pylori in the pathogenesis of PUD is well established and it is now widely accepted that Helicobacter pylori eradication therapy should be offered to all patients with documented infection. The ideal treatment, with an eradication rate approaching 100% and low incidence of side effects is yet to be identified. Treatment success is related to various factors like patient compliance, bacterial resistance to antibiotics, treatment duration and antibiotic related side effects. To address these challenges, simpler eradication regimens and new antibiotic combinations are required.[5-8]

The present study was designed to ascertain if levofloxacin, a newer quinolone, in conjunction with azithromycin, a macrolide, along with a PPI, in a once daily regimen was therapeutically equivalent to the conventional triple therapy of clarithromycin, amoxicillin and a PPI, in the eradication of Helicobacter pylori. Both levofloxacin and azithromycin exert a high anti-Helicobacter pylori activity and require a once daily dosage on the basis of their pharmacokinetic properties. Data available show that the minimum inhibitory concentration of these antibiotics against Helicobacter pylori is <0.005ug/ml; which is almost similar to that of amoxicillin and clarithromycin.[9-12]

Levofloxacin, in association with other antibiotics has shown eradication rates higher than 90% with a low incidence of side effects, in first line therapy[5]. Similarly, azithromycin which is used as the clarithromycin substitute has achieved an eradication rate of 72 – 88%86. Esomeprazole was used on account of its better and more rapid acid suppression profile than omeprazole.[13-15]

In the present study, there was a slight male preponderance. Similar finding has been reported in a meta-analysis. There was another study which showed a female preponderance [16-17]. However, the role of gender as a risk factor is still debated.

In India, 64% – 90% of duodenal ulcers, 50% – 65% of gastric ulcers and 42 – 74% of NUD cases are associated with Helicobacter pylori infection24. Similarly in our study, patients with PUD constituted a majority (77.8%), followed by GERD (15.3%) and NUD (6.9%). Three patients were lost to follow up (2 – ELA group, 1 – ECA group).

In patients with investigated NUD, it has been proved that eradication of Helicobacter pylori is beneficial18-19. Though there has been a negative association of Helicobacter pylori, in patients with GERD, it has been suggested that eradication should be considered in patients receiving long term maintenance treatment with PPIs.[18-19]

The highest number of Helicobacter pylori positive patients was in the age group 25 – 55 years. This was in concurrence with the finding that the prevalence among middle-aged adults is over 80% in developing countries compared to 50% in industrialized countries[20-21].

Pain abdomen was the most common presenting complaint in both the groups, followed by regurgitation, nausea and bloating (Table 4). Both the treatment groups matched in terms of duration of symptoms. Majority of the patients were symptomatic for a duration ranging from 1 month-1 year.

Compliance was assessed in 69 patients, who completed the study. Two patients in the ELA group had poor compliance, as compared to 1 patient in the ECA group. This was in contrast to a similar study, which reported lower incidence of poor compliance to levofloxacin based regimen as compared to the standard triple drug regimen[22-23]. In the present study, poor compliance was mainly due to side effects of the prescribed drugs.

A total of 16 patients experienced side effects. Majority of the patients had mild to moderate side effects. Only one patient in the ELA group developed skin rash after 4 days of drug intake, following which the treatment was stopped. Diarrhoea was the most common side effect in the ECA group, whereas taste disturbance was seen more frequently in the ELA group. All the side effects disappeared spontaneously within 7 days after stoppage of the drug. Tolerability was analyzed in all compliant patients and was found to be similar in the two groups.

Improvement in the symptoms was almost the same in the study groups. In the ELA group, 29 (85.3%) of the 34 patients experienced an improvement in their pre- treatment symptoms, while 5 (14.7%) felt their symptoms were unresolved or even worsened. In the ECA group, 33 (94.3%) patients had their symptoms resolved and only 2 (5.7%) patients had unresolved symptoms.

Lesion healing rate was better with ECA therapy (77.1%) than with ELA therapy (61.76%). But this difference was not statistically significant.It has been proposed that, an ideal eradication regimen must have cure rates of at least 80% (according to intention-to-treat analysis), without major side effects and with minimal induction of bacterial resistance[17].

In the present study, the eradication rate was 67.6% with the ELA group in comparison to 77.1% with the ECA group. Similar eradication rates for the triple drug regimens (ELA – 70%, ECA – 76%) has been reported 90. In other studies where levofloxacin has been used as first line therapy (along with rabeprazole and nitroimidazole,), as second line therapy or as rescue therapy, eradication rates of >90%, 86.9% and 81% has been reported respectively.

It is important to point out that the eradication rates of both the triple drug regimens are low in the present study as compared to other studies[24]. The PPI used in the present study, esomeprazole has a higher oral bioavailability, than that of omeprazole; which results in greater acid suppression. The dose of 20mg esomeprazole used in the once daily regimen should not be regarded as a possible cause of an inadequate inhibition of gastric acid secretion, and in turn, an inappropriate activity of antibiotics. This is because, levofloxacin has a constant solubility at gastric pH of 0.6-5.8 and has an absolute bioavailability of approximately 99%, whereas azithromycin is an acid stable antimicrobial agent, with extensive tissue distribution. Moreover, a study which compared 20 mg esomeprazole with 40 mg esomeprazole in 38 patients with GERD, once daily for 5 days showed that esomeprazole, at either dose, was effective in terms of maintaining adequate gastric pH, for a longer period of time.[20-25] Therefore it is likely that eradication rate of anti-Helicobacter pylori regimens is dependent on the antimicrobials used and not on the dose of the proton pump inhibitor.

Primary antibiotic resistance will be a problem as more and more patients receive eradication therapy containing various antimicrobials. As a result, antibiotic sensitivity testing will play a greater role in the future of eradication of Helicobacter pylori infection. Till then, the search for improved and simplified treatment regimens continues.

Conclusion

The present study demonstrates that once-daily levofloxacin plus azithromycin based triple therapy achieves Helicobacter pylori eradication rate comparable to that of the standard, twice-daily triple therapy. Patient compliance, drug tolerability and side effects profile were almost the same in the two treatment groups. Hence levofloxacin-based triple therapies may represent a promising, alternative therapeutic option in the first-line therapy for Helicobacter pylori infection.

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