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A RANDOMIZED COMPARATIVE STUDY OF LEVOFLOXACIN BASED TRIPLE THERAPY WITH STANDARD TRIPLE THERAPY FOR *HELICOBACTER PYLORI* ERADICATION

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ABSTRACT

Helicobacter pylori are associated with peptic ulcer disease, gastritis and malignancy. Eradication of *Helicobacter pylori* in patient with peptic ulcer greatly reduces the rate of relapse. Hence, it is vital to find the ideal regimen. Primary antibiotic resistance and poor compliance attribute to eradication failure of standard regimens. This study investigated the eradication rate, patient compliance, tolerability and side effects profile of a one week, once daily levofloxacin plus azithromycin triple therapy versus standard twice daily triple therapy. A prospective, randomized, comparative study, enrolling 72 *Helicobacter pylori* positive patients, with dyspeptic symptoms was done. These patients were randomized either to the esomeprazole 20 mg, levofloxacin 500mg, and azithromycin 500mg, once daily (ELA Group) or esomeprazole 20mg, clarithromycin 500mg and amoxicillin 1 gm twice daily (ECA group) for 1 week. Helicobacter pylori infection was defined by rapid urease test and histology, both at the entry, as well as at the end of the study. Helicobacter pylori eradication rates of ELA and ECA group were similar (67.6% and 77.1% respectively, p=0.337). Both the treatment groups were similar in terms of compliance (p=0.721) and tolerability (p=0.963). No significant differences were noted in the incidence of side effects between the two treatment groups (p=0.253). Once daily, levofloxacin plus azithromycin-based triple therapy may represent a promising alternative to the standard twice daily triple therapy.

Keywords: *Peptic ulcer; H.pylori; Levofloxacin; Azithromycin; Triple therapy.*

INTRODUCTION

For many decades the dictum 'No acid, No ulcer' dominated thinking on the pathogenesis of Peptic ulcer. Around 25 years back, Marshall, a clinician, collaborating with Warren, a pathologist, made the seemingly simple observation that "curved bacilli" (now named *Helicobacter pylori*) are more common in the stomach of patients with "chronic active gastritis" than in control patients[1]. The discovery of *Helicobacter* provides a number of lessons worth emulating: the seminal link between bacterial infection and disease was made by clinically oriented physicians; simple laboratory and statistical techniques established the association; the initial connection made was between *Helicobacter* and a condition that is clinically insignificant (nonerosive gastritis), yet the discovery evolved dramatically to improve the diagnosis and treatment of a common disease with significant mortality and morbidity (peptic ulcer), and the time between the first reported isolation of *Helicobacter* and translation of the discovery to provide practical benefit for patients, was less than 1 decade. It is now understood that *Helicobacter* infects the stomach of about 90% of patients with duodenal ulcers, and that eradicating *Helicobacter* cures these ulcers with a recurrence rate of less than 10% compared with gastric acid reducing treatments, which lead to an ulcer recurrence rate of over 70%.[2]

More than 10 years following the initial report of *H. pylori* gastritis, the National Institutes of Health, USA, recommended *H. pylori* eradication as the standard of care in treatment of duodenal ulcer (DU) and gastric ulcer (GU) associated with *H. pylori* infection[3]. The strongest indication for eradication of *H. pylori* is in patients with duodenal ulcer; 90%-95% of Indian subjects with duodenal ulcer are positive for *H. pylori* compared to 80% of asymptomatic healthy individuals in the community.[4] Elegant studies from the West showed that eradication of *H. pylori* resulted in healing of ulcer, and that *H. pylori*-related DU did not recur unless there was recurrence (either recrudescence or re-infection) of the infection. Thus, Marshall *et al* showed that *H. pylori* eradication resulted in greater DU healing rate (92% vs. 61%) and lower 12-month relapse rate (21% vs. 84%) than non-eradication.[5].

The optimal treatment regime for the eradication of *H. pylori* has not yet been defined, but the treatment which is effective in developed countries may not be suitable for patients in the developing world like India. The reason being that, the environment in India is contaminated and gastrointestinal infections –

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symptomatic and asymptomatic – are very common. Secondly, antibiotic use or misuse is widely prevalent; the resultant high frequency of antibiotic resistance implies that treatment regimens for *H. pylori* eradication may not be effective.

The attempted eradication of *H. pylori* with antibacterial monotherapy has not been encouraging. The highest eradication rates of monotherapy are achieved with a bismuth compound (20%) and amoxicillin (23%)[6]. Most dual therapies, such as bismuth - amoxicillin, bismuth-metronidazole and amoxicillin - metronidazole, achieve eradication in less than 55% of cases[6]. Different treatment regimens for the eradication of *H pylori have* been widely sought, and the treatment currently recommended by the National Institute of Health Consensus is bismuth based combination therapy that includes a nitroimidazole and a second antibiotic all given for 14 days. Average eradication rates have been reported as 73% in studies using amoxicillin as the second antibiotic and 82 % in studies using tetracycline as the second antibiotic[7].The clinical efficacy of these regimens can be less than optimal in some patient population due to several factors, including antibiotic resistance and lack of compliance. In particular, bismuth based regimen that include a nitroimidazole show decreased efficacy against metronidazole – resistant *H. pylori*[8,9]. A high incidence of side effects with this treatment, however, has encouraged researchers to identify regimens which are as effective, less complex, with fewer side effects, and of shorter duration, thereby encouraging compliance. Use of triple therapy regimens combining two antibiotics with a proton pump inhibitor has gained wide spread attention over the past 3 years. Interest in such combination therapy was spurred by Bazzoli et al[10] who presented results suggesting that a 1 week treatment with clarithromycin, tinidazole, and omeprazole produced a 95% eradication rate of *H.pylori* infection, with negligible side effects. Subsequent to the reported success of this therapeutic strategy, a number of abstracts have suggested that therapeutic regimens including clarithromycin and a proton pump inhibitor in combination with amoxicillin or a nitroimidazole achieve eradication rates against *H. Pylori* that may exceed 90% [11-13] .

Clinical trials are undertaken to search for simpler but equally effective (or more effective) regimen. A number of antimicrobial agents have been used in various regimens to eradicate *Helicobacter pylori*. The properties of different medications may have some impact on the therapy result. Levofloxacin is an isomer of ofloxacin with a broad spectrum of activity against several gram positive and gram negative bacteria. Its antibacterial activity is based on the inhibition of bacterial Topoisomerase IV. It is quickly absorbed with an oral bioavailability of 100%, Plasma half life of 9 – 16 hrs and a predominant renal excretion. In association with other antibiotics, levofloxacin has eradication rates higher than 90% with low incidence of side effects in first line, second line and rescue therapy[14]. Azithromycin is one of the newer, orally administered macrolide antibiotics. Like clarithromycin, it is also acid stable. Azithromycin is well absorbed from the gastrointestinal tract and extensively distributed in tissues. It has long elimination half life, which increases on subsequent dosing. After an initial oral dose of 1000mg, followed by 500mg/day for 5 days, the elimination half life has been reported to be 57 hours[15]. Azithromycin has an excellent *in vitro* activity against *Helicobacter pylori, in vivo*, it is not effective as a single agent because of acquired resistance. However, when used in combination with other antibiotics, improved eradication rates are achieved[16].

The present study was designed to ascertain if Levofloxacin, a newer quinolone, in conjunction with Azithromycin, a macrolide, along with a PPI in once daily regimen was therapeutically equivalent to the Conventional triple therapy of clarithromycin, amoxicillin and PPI in eradication of *Helicobacter pylori*.

MATERIALS AND METHODS

It is an open labelled, randomized study conducted on 72 subjects attending the out patient department of gastroenterology, in a tertiary care centre. The study was conducted for a period of one year starting from Nov 2005 – Oct 2006. Subjects of either sex aged 18-60 years with dyspeptic symptoms were included in the study. Subjects on NSAIDS, anticoagulants, corticosteroids were excluded from the study. Subjects with co morbid condition like IHD, congestive cardiac failure, renal failure, portal hypertension, any malignancy or any evidence of gastrointestinal bleeding and female subjects who were pregnant or lactating were also excluded from the study. Informed consent was obtained after fully explaining the procedure and the consequences, in patient's own language. The work up included a detailed history taking, symptom analysis and clinical findings. History of habits, family history and drug history were taken as they have a direct bearing on peptic ulcer disease (PUD). After an overnight fast, all patients under went upper GI endoscopy. Mucosal specimens were obtained from each of the patients, from the antrum and the gastric body for the detection of *H. pylori* using biopsy forceps. *H. pylori* infection at the time of entry was determined by rapid urease test and histological assessment of mucosal specimen. Two biopsy specimens, one each from the antrum and corpus were placed in 2% christnsen'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 rapid urease test (RUT) indicative of *H. pylori* infection. The histological assessment of *H. pylori* status was performed using biopsy specimen stained with Giemsa. Subjects were considered to be positive for *H. pylori* only when both the rapid urease test and the histological examination showed positive results for *H. pylori*. Subjects initially

classified as positive for H. Pylori on the basis of the RUT were reclassified as negative if the histology report came negative for the same.

Patient were randomized according to a computer generated randomization schedule, to receive a 7 days treatment with either esomeprazole 20 mg, levofloxacin 500mg, and azithromycin 500mg, once daily (ELA)or esomeprazole 20 mg, clarithromycin 500mg and Amoxicillin 1 gm 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 scale [17] (Excellent – drug taken for 7 days, Good - drug taken for 5 - 6 days, Poor - drug taken for < 5 days). Incidence of side effects was checked using a standardized questionnaire[18] given to the patient at the time of enrolment and to be filled during treatment period, indicating the type and degree of interference with daily activity of the patients as follows: A = No side effects, B = Slight discomfort, not interfering with daily activity, C = Moderate side effect, sometime interfering with daily activity, D = Severe side effects, work not possible, & E = Side effects severe enough to discontinue treatment. Tolerability was analysed in all compliant patient based on the side effects grading. The patient assigning themselves to group A or B were considered to have tolerated the treatment well, while assignment to group C, D, E indicated poor tolerance.

Follow up – 2: Four to six weeks after conclusion of therapy, an endoscopy, RUT and biopsy (as at entry) were performed in all patients.

Clinical response: Symptoms of abdominal pain, bloating or postprandial fullness, and belching, acid reflux and heart burn 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 was same or even worsened.

RESULTS

Subjects were randomized from Nov 2005 - Oct 2006. A total of 72 *H. pylori* positive subjects were enrolled into the study, 36 were randomized to ELA group and 36 to the ECA group. Three subjects were lost to follow up, 2 from ELA group and one from ECA group. Complete data was available for 34 subjects in ELA group and 35 subjects in ECA group. The groups were well matched with respect to age, sex, diet, habits, co-morbid conditions and type of diseases.

Data regarding the demographic characteristics of the patients at entry are summarized in Table 1. Mean age of patients was found to be 45.5 years with a standard deviation of 14.59 years. There is slight male preponderance with male: female ratio of 2.4:1. Majority of the subjects (82%) didn't have any other co morbid condition. With respect to habits 57% had no history of any habits while 18% of subjects reported history of taking alcohol.

Table 1. Characteristics of the study population

Parameters	Treatment A ELA	Treatment B ECA	Total (mean – SD)	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	1(2.85%)	1(2.8%)	2(2.8%)	0.733
Hypertension	3(8.3%)	3(8.3%)	6(8.3%)	
Diabetes+ Hypertension	1(2.8%)	3(8.3%)	4(5.6%)	
Epilepsy	1(2.8%)	-	1(1.4%)	
Lost to follow - up	2(5.65)	1(2.8%)	3(4.2%)	-

Both the treatment groups matched with respect to age, gender, diet, habits, and co-morbid conditions. Male: Female ratio was – 2.4:1

Pain abdomen is the commonest clinical presentation in both treatment group, next followed by regurgitation (36%) in ELA group and nausea (30%) in ECA group. 38 subjects (53%) were symptomatic for a duration ranging from 1 month – 1 year, followed by 22 (31%) who had symptoms for 1–5 years.

Table 2 shows the distribution of clinical response at the end of the study according to the initial severity of the symptoms. Twenty nine (85.3%) subjects in the ELA group, 33 (94.3%) subjects in ECA group experienced an improvement in the severity of the symptoms, whereas 5 (14.7%) subjects in the ELA group and 2 (5.6%) subjects in the ECA group felt that the symptoms were unresolved or even worsened. In ELA group the endoscopic lesions were completely healed in 21 (61.76%) cases as compared to 27(77.1%) cases in the ECA group (Figure 1). *H. 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) (Figure 2). Compliance analyzed in 69 subjects, showed that 91% of subjects had excellent compliance (drug taken for 7 days) in both the arms of the study. Two subjects in ELA group arm had poor compliance as compared to 1 in ECA group arm.

Table 2. *Distribution of Clinical response at the study according to the initial severity of the symptom*

Treatment	Symptoms Severity	Resolved /Improved	Unresolved /Worsened	Total	p value
ELA	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
	Mild	13(100%)		13	
ECA	Moderate	17(89.5%)	2(10.5%)	19	
	Severe	3(100%)		3	
	Total	33(94.3%)	2(5.7%)	35(100%)	0.409

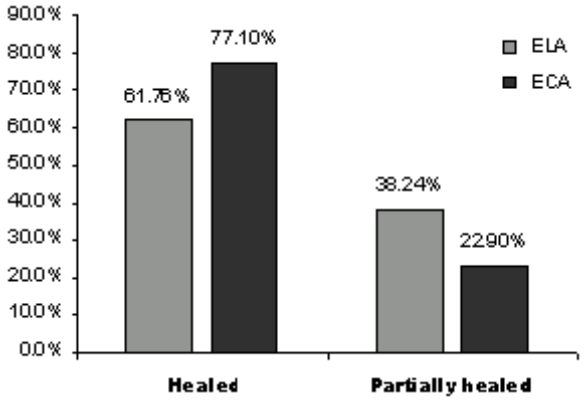

Fig. 1. *Distribution of endoscopic lesion healing rates*

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. ($X^2 = 2.32$, $p = 0.127$)

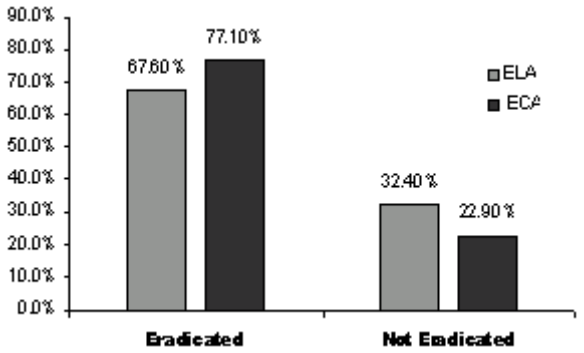

Fig. 2. *Distribution of Eradication rate*

H. Pylori infection was eradicated in 23 (67.6%) cases, in the ELA group, where as the eradication rate with the ECA group was 77.1% (27 cases) ($X^2 = 0.779$, $p=0.377$)

A total of 16 subjects experienced side effects. Majority of the subjects had mild to moderate side effects. Only one subjects in the ELA group arm developed skin rashes after 4 days of drug intake. Diarrhoea was the most common side effect in the ECA group arm whereas taste disturbance was seen more frequently in the ELA group arm. Tolerability was analyzed in all compliant patients and was found to be similar in the two groups (Table 3)

Table 3. Assessment of tolerance

Tolerance	ELA	ECA	Total
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%)

$X^2 = 0.076$, $p = 0.963$

DISCUSSION

In the present study, there is slight male preponderance. The role of gender as a risk factor is still debated topic as some studies report male [19, 20] where as few other report female preponderance [21]. In India, 64% - 90% of duodenal ulcers, 50% - 65% of gastric ulcer and 42% - 74% of NUD cases are associated with *Helicobacter pylori* Infection [22]. The highest numbers of Helicobacter pylori positive subjects were in the age group of 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 [23].

Incidence of poor compliance was lower, although not significant, in patients randomized to ECA than to ELA (6% versus 3%). 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 [24].

In the present study, the eradication rate was 67.6% with ELA group in comparison to 77.1% with ECA group. Similar eradication rate for the triple drug regimens (ELA – 70%, ECA – 76%) has been reported [24]. 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 rate of >90% [25], 86.9% [26], 81% [27]

It is important to point out that the eradication rates of both the triple drug regimen are low in the present study as compared to other studies [25, 28, 29]. 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 20 mg esomeprazole used in the once daily regimen should not be regarded as 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%[24], whereas azithromycin is an acid stable antimicrobial agent, with extensive tissue distribution[24, 30]. Moreover, a study which compared 20 mg of 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 longer period of time [31]. 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 PPI.

Till recent years, primary resistance to levofloxacin was not reported, although the prevalence of secondary resistance was estimated to be about 31% after two eradication attempts [32]. But recent data has shown that primary resistance to levofloxacin could be as high as 20% in some geographical areas [33, 34]. This is because quinolones are being frequently over prescribed for many infections, leading to primary resistance, which could result in low eradication rates. Similarly primary azithromycin resistance has been reported in 10% - 12% of cases. Resistance to clarithromycin and amoxicillin has been reported to be 10.1% to 12% and 1.4% respectively. Primary antibody resistance will be

a problem as more and more patients receive eradication therapy containing various antimicrobils. This suggests the need for an antimicrobial susceptibility testing, at least in areas where there is rampant usage of these drugs.

CONCLUSION

From the present study, it is evident that once daily, seven days regimen containing a PPI in combination with levofloxacin and azithromycin is as efficacious and well tolerated as the standard twice daily triple therapy. Moreover, the advantage with the ELA regimen is the reduced number of tablets the patient is required to take.

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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