Original Article

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Internal Medicine Section

Clarithromycin versus Levofloxacin Based Triple Drug Therapy as First Line Eradication for *Helicobacter pylori* Infection- A Randomised Clinical Study

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ABSTRACT

Introduction: *Helicobacter pylori (H. pylori)* are microaerophilic gram negative, spiral shaped, flagellated bacterial pathogens transmissible to humans. The prevalence of infection with *H. pylori* infection varies worldwide. Pharmacologic therapy for eradication must be initiated in symptomatic individuals with emphasis on hygiene and sanitation. The high prevalence of *H. pylori* infection in the country, and the lack of adequate evidence on the efficacy of the standard triple therapy in Southern India was the drive to conduct this study.

Aim: To compare and evaluate the efficacy of 14 days clarithromycin based triple drug therapy over 10 days levofloxacin based triple drug therapy in *H. pylori* eradication.

Materials and Methods: A randomised clinical study was conducted from September 2018 to February 2019, at a tertiary care teaching hospital and research centre in suburban Chennai, Southern India. Eighty patients with dyspepsia, who were diagnosed with *H. pylori* infection based on both Rapid Urease Test (RUT) and histopathology of antral biopsy, were alternately assigned to treatment with either 14 days clarithromycin based triple drug regimen (PAC) or 10 days levofloxacin based triple drug regimen (PAL). Efficacy of the drugs were compared using both RUT and histopathology of endoscopic antral biopsy specimen four weeks after completion of the treatment. Chi-square test was used for data analysis.

Results: Out of the 80 enrolled patients, 70 individuals completed the study, of which 41 were males and 29 were females. Baseline characteristics were similar in the both the groups-mean age 42.31±14.8 years in PAC and 42.20±12.67 years in PAL (p=0.150); 65.7% were males and 34.3% were females in PAC group, 51.4% were males and 48.6% were females in PAL group (p=0.225). Clearance of infection was seen in 23 patients (65.7%) in PAL group as compared to 32 patients (91.4%) in the PAC (p=0.01). Among patients with failure of eradication, 3 (1.05%) from PAC group and 12 (4.20%) from PAL group had persistence of dyspeptic symptoms. In addition, 7.14% (5 out of 70-two from PAC and three from PAL group) of subjects who had *H. pylori* eradication had persistence of same symptoms of dyspepsia on follow-up at four weeks after completion of the regimen.

Conclusion: A 14 days clarithromycin based triple drug regimen is more effective than 10 days levofloxacin based triple drug regime for the eradication of *H. pylori* infection.

Keywords: Dyspepsia, Histopathology, Rapid urease test

INTRODUCTION

H. pylori infection in man has been in existence since the dawn of time. In developing countries with poor sanitary conditions, it causes persistent infection and low-level disease, acting more like a commensal rather than a pathogenic organism [1]. Prasad S et al., in a southern India cohort, showed that *H. pylori* was detected in the gastric mucosa of 83.3% healthy volunteers. They also showed high prevalence rate in subjects with gastroduodenal disease viz duodenal ulcer (92.6%), gastric ulcer (81.3%), and (71.4%) in non ulcer dyspepsia [2]. As the *H. pylori* strains are genetically diverse, it is likely that most infected individuals in the community have less virulent strains [3]. Also, excess gastric acid secretion caused by *H. pylori* may be protective, as it acts as a barrier to ingested pathogens [3]. Until a better knowledge is acquired and understanding of the nature of the *H. pylori* infection in humans, its indiscriminate eradication in asymptomatic individuals is likely to do more harm than good [3]. *H. pylori* primarily colonises the upper gastrointestinal tract, causing progressive acute and chronic gastric and duodenal inflammation. Typically, these pathologic changes do not cause symptoms, but clinical disease manifestations occur in approximately 20% of the infected, usually after a long latent period [4].

H. pylori infection can cause gastritis, duodenal ulcer disease, gastric ulcer disease, gastric atrophy, gastric adenocarcinoma, primary gastric B-cell lymphoma, vitamin B12 deficiency and iron deficiency anaemia [5,6]. The outcome of an *H. pylori* infection is determined by a complex interplay of host, environmental and bacterial factors including the virulence of the infecting bacterial strain. Current gold standard to diagnose the infection in India is by performing endoscopic gastric biopsy for histology and RUT [7]. Selection of drug regimens for *H. pylori* infection are influenced by patient tolerance, efficacy, and existing antibiotic resistance. The treatment goal is to choose a regimen that will reliably produce high treatment success [8]. Standard regimen using clarithromycin plus Proton Pump Inhibitor (PPI) plus amoxicillin or metronidazole for 14 days is the preferred first-line treatment regimen in areas with low clarithromycin resistance.

Studies from India has showed high antibacterial resistance to most commonly used anti *H. pylori* regimen, viz., amoxicillin, clarithromycin, and metronidazole [9]. The levofloxacin based regime is considered as a salvage regimen in those not responding to the standard triple drug regime comprising a PPI, clarithromycin and amoxicillin or metronidazole. Having broad antimicrobial activity, fluroquinolones are also widely used to treat a variety of other bacterial infections [10]. Widespread use of fluroquinolones in the treatment of community-acquired bacterial infections has led to the marked emergence of fluoroquinolone resistant *Mycobacterium*

tuberculosis in many countries [11]. Being highly prevalent in India, it is likely that *H. pylori* infection may also have decreased response to levofloxacin based regime due to resistance. Hence, levofloxacin based regime was chosen to study if it can justify its label of salvage/rescue regime.

Also, there is lack of literature studying efficacy of two different drug combinations in eradication of *H. pylori* in a given population in Southern India. The high prevalence of *H. pylori* infection in this population and the lack of adequate evidence on the efficacy of the standard triple therapy in the study cohort was the drive to conduct this study. This study aimed at the evaluation of efficacy of two different regimes viz clarithromycin based regime and levofloxacin based regime, in the eradication of *H. pylori* infection. The secondary objective was resolution of symptoms of dyspepsia.

MATERIALS AND METHODS

A randomised clinical trial was conducted at the Department of Medical Gastroenterology, SRM Medical College Hospital, Kattankulathur, Chengalpattu, Tamil Nadu, India, between September 2018 and February 2019. The protocol was approved by the Institutional Ethical Committee (IEC) (IEC approval number- 1455/IEC/2018). Patients were included in the study after obtaining written informed consent and were selected based on the inclusion and exclusion criteria.

Inclusion criteria: Age group 18-60 years, both genders, with symptoms of dyspepsia, including epigastric pain syndrome (epigastric burning and/or pain) and/or postprandial distress syndrome (fullness and/or meal-related early satiation), with endoscopic evidence of gastritis or gastric ulcer or duodenal ulcer, positive for H. pylori (both RUT and histopathology) were included in the study.

Exclusion criteria: Subjects who had undergone a previous eradication therapy or had a known history of hypersensitivity to penicillin group of drugs, quinolone and/or macrolide antibiotics were excluded from the study.

Sample size calculation: Sample size was calculated using the following formula:

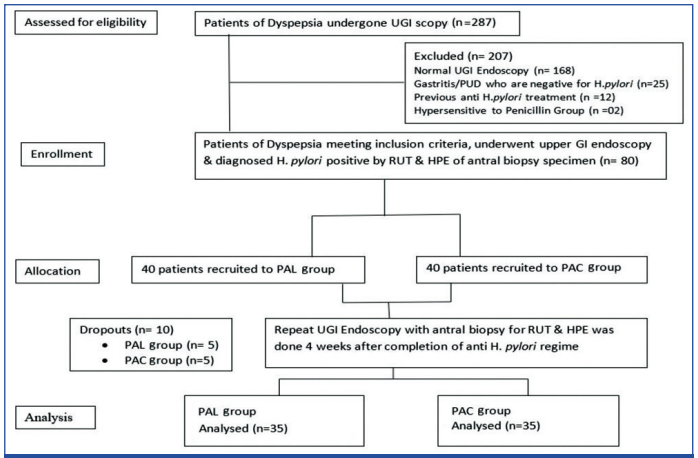
$n=Z^2 \times p\hat{}(1-p\hat{})/E^2$, where

n, is the required sample size which was 68, Z is the z score at 85% confidence level, p^ is the population proportion derived from 80% or more prevalence of *H. pylori* infection in Indian rural population [1], E is the margin of error 7%. The hospital, being located in suburban region and catering primarily to a rural population, a total of 80 *H. pylori* positive patients were enrolled, of which there were 10 dropouts during the study.

Study Procedure

A total of 287 patients underwent upper gastrointestinal endoscopy for evaluation of dyspepsia. Gastric antral biopsies were taken if any of the above findings was seen. Slide based RUT along with histopathologic examination to detect *H. pylori* were performed with the antral biopsy specimens. Patients were regarded as *H. pylori* positive if both tests were positive.

Systematic randomisation was done in two groups where alternate patients were assigned to each group. The PAC group received 14 days clarithromycin based triple drug therapy (clarithromycin 500 mg twice a day, amoxicillin 1 gm twice a day, pantoprazole 40 mg twice a day). The PAL group received 10 days levofloxacin based triple drug therapy (levofloxacin 500 mg once a day, amoxicillin 1 gm twice a day, pantoprazole 40 mg twice a day). A repeat upper gastrointestinal endoscopy, RUT and histopathologic examination of antral biopsy specimen was done four weeks after the completion of the drug regime. Eradication of *H. pylori* was documented in those in whom both RUT and histology were negative after four weeks. The investigator interpreting the RUT result, the pathologist performing histologic examination of biopsy specimen, and the person analysing the data were blinded to the treatment regime used [Table/Fig-1].



[Table/Fig-1]: CONSORT flowchart.
RUT: Rapid urease test; HPE: Histopathologic examination; n: Number; UGI: Upper gastrointestinal

STATISTICAL ANALYSIS

Results were analysed by the graph pad prism version 6.01software and data was presented as means±Standard Deviation (SD). Chi-square method was used for the comparison between two study groups. The p-values <0.05 was considered statistically significant.

RESULTS

A total of 80 patients were selected for the study. The reasons for the dropout were gastrointestinal intolerance in eight patients in the form of vomiting (three in PAC group, two in PAL group), diarrhoea (one in PAC group, one in PAL group), worsening of epigastric pain (one in PAL group), two patients lost to follow-up (one in each group). Hence, the total number of subjects in this study was 70 (35 in each group).

There was no statistically significant age or gender difference between two study groups, with the mean age 42.31±14.8 years in PAC and 42.20±12.67 years in PAL group (p=0.150). Overall, 65.7% were males and 34.3% were females in PAC group; 51.4% were males and 48.6% were females in PAL group (p=0.225) [Table/Fig-2]. There was a significant difference in the eradication rate between the two study groups [Table/Fig-3]. There were no serious adverse events like anaphylaxis, hepatitis, pancreatitis, seizures or Stevens-Johnson syndrome (SJS) in the study participants. Minor adverse effects like nausea, and diarrhoea were encountered by 5 (14.2%) patients in PAC group and 4 (11.4%) patients in PAL group.

Parameters		PAC	PAL	Chi-square	p-value
Gender	Male	23 (65.7)	18 (51.4)	1.471	0.225
	Female	12 (34.3)	17 (48.6)		
Age (years)	18-30	7 (20)	5 (14.3)	5.315	0.150
	31-40	12 (34.3)	10 (28.6)		
	41-50	4 (11.4)	12 (34.3)		
	>50	12 (34.3)	8 (22.8)		

[Table/Fig-2]: Baseline demographics of study participants.

Drug group	Responders	Non responders	Chi-square	p-value
PAC	32 (91.4)	03 (8.6)	5.43	0.01
PAL	23 (65.7)	12 (34.3)		

[Table/Fig-3]: Comparison of eradication with respect to response obtained based on RUT and HPE.

Among patients who had successful *H. pylori* eradication, 7.14% subjects (5 out of 70) had persistence of same symptoms of dyspepsia (two had epigastric burning, two patients had postprandial distress and one patient had both epigastric burning and postprandial distress) even after eradication of *H. pylori*. All patients who had failure of *H. pylori* eradication continued to have dyspeptic symptoms [Table/Fig-4].

Symptoms	Group	Treatment outcome	No. with symptom before treatment	No. with symptom after treatment	Number (%) of subjects with symptom resolution	Chi-square	p-value
Epigastric pain or burning	PAC	Success	11	1	10 (90.9%)	1.17	0.27
		Failure	1	1	0		
	PAL	Success	7	1	6 (85.7%)		
		Failure	7	7	0		
Postprandial fullness/bloat	PAC	Success	6	1	5 (83.3%)		
		Failure	1	1	0		
	PAL	Success	5	1	4 (80%)		
		Failure	2	2	0		
Combination of above symptoms	PAC	Success	15	0	15 (100%)		
		Failure	1	1	0		
	PAL	Success	11	1	10 (90.9%)		
		Failure	3	3	0		

[Table/Fig-4]: Comparison of symptom resolution before and after treatment.

DISCUSSION

Treatment of *H. pylori* consists of a combination of antibiotics and PPI. PPIs also have an anti *H. pylori* activity, and decrease the load of *H. pylori* [12]. The available data from India do not provide the information needed to prospectively identify a successful treatment regimen. Pandya HB et al., showed high prevalence of *H. pylori* resistance to amoxicillin (72.5%), clarithromycin (58.8%), and levofloxacin (13.8%) in their study from Gujarat [9]. Similarly, Wani FA et al., showed a high *H. pylori* resistance to clarithromycin (45%), and metronidazole (81%) in a population from Kashmir [13]. Thyagarajan SP et al., in a multicentred study in India showed *H. pylori* resistance rate was 77.9% to metronidazole, 44.7% to clarithromycin and 32.8% to amoxycillin. They showed that rate of resistance was higher in southern India than in northern India [14].

A systematic review of published literature on *H. pylori* antibiotic resistance, concluded that the resistance pattern of *H. pylori* is increasing worldwide. It showed prevalence of both clarithromycin and levofloxacin resistance at around 30% in Asian population [15]. Finding an antibiotic combination, with least resistance, is crucial for successful eradication of *H. pylori*. The success of treatment depends on patient compliance, right dose and duration and prevalence of resistant bacterial strain in the population. Gehlot VA et al., carried out a study in North India on *H. pylori* strains, which were cultured and then tested for resistance by agar-dilution method [16]. Resistance to levofloxacin was found in 73.2% (41/56; Minimum Inhibitory Concentration (MIC) >1 µg/mL) of the isolates. Similarly, Shetty V et al., showed that 55% of *H. pylori* isolates were resistant to levofloxacin in a study conducted in Karnataka, India [17]. These findings were similar to the present study data which showed treatment failure in 34.3% among the levofloxacin group. However, Federico A et al., conducted a study in Italy, and reported that 5-Day levofloxacin- containing concomitant therapy achieved 90% cure rate in patients who were clarithromycin resistant [18].

A prospective single centre study from Spain showed that the eradication rates were better with levofloxacin triple drug regime comprising levofloxacin, amoxicillin and omeprazole (80%), compared to standard clarithromycin triple drug regime (64%) [19]. Gisbert JP et al., found that levofloxacin (500 mg b.d.), amoxicillin (1g b.d.) and ranitidine bismuth citrate (400 mg b.d.) for 10 days as first line regime, achieved *H. pylori* eradication in 88.5% subjects [20]. In a meta-analysis of seven studies from different parts of the world by Peedikayil MC et al., showed comparable eradication rate between levofloxacin group 79.05% versus 81.4% in the standard group with clarithromycin regime [21]. Another recent meta-analysis involving 13 studies in Iran showed that the *H. pylori* eradication rate was significantly higher in patients receiving levofloxacin compared with clarithromycin (75.2% vs. 66.3%) [22].

Therefore, evidence available from one geographical region may not be useful in determining treatment in another geographical region, due to variation in bacterial resistance pattern. Hence this study was conducted to compare the efficacy between clarithromycin based triple therapy and levofloxacin based triple therapy in the eradication of *H. pylori* in a southern Indian population. Patients who were residents of suburban Chennai, and adjoining Chengalpattu district were recruited for the study. Statistical data showed a significant difference in eradication rate between two groups, with clarithromycin (91.4%) showing better efficacy compared to levofloxacin (65.7%).

Though levofloxacin based triple therapy have shown good eradication rate in other countries and also in certain regions of India, this cannot be generalised to entire country as resistance occur unevenly due to large size of the Indian nation and its associated socio-economic differences. Another possible cause for the decreased efficacy of levofloxacin triple therapy could be the empiric use of levofloxacin with good success for other bacterial infections [23], wherein this widespread use could have led to inadvertent *H. pylori* resistance over years as this organism is widely prevalent in India. Due to lack of similar studies in this geographical area, multicentric randomised control studies, involving larger number of populations are needed.

Limitation(s)

Being a time bound study in the setting of academic trial, an in-vitro study of resistance of *H. pylori* isolates could not be done, which in turn would have provided direct evidence of antimicrobial resistance pattern.

CONCLUSION(S)

The study suggests that levofloxacin resistance is much higher than clarithromycin resistance in this south Indian cohort. There was no difference between two groups in terms of symptom resolution in those who had successful eradication. 7.14% subjects with successful eradication had persistence of dyspeptic symptoms which was probably attributable to underlying functional dyspepsia. None of the patients with failure of eradication, which was higher in PAL group showed symptom resolution. Therefore, levofloxacin based regime may not be an ideal rescue treatment in patients who fail clarithromycin based regime. An ideal second line/rescue antibiotic regime in patients who fail first line therapy with clarithromycin regime needs to be explored.

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