

Helicobacter Pylori Sequential Eradication Therapy: Clarithromycin based Therapy Versus Levofloxacin based Therapy. Study from Kashmir Valley

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ABSTRACT

Introduction: Various regimens have been used for H-pylori eradication. Sequential therapy is an alternative to classical triple therapy. This study was designed for evaluating the efficacy of levofloxacin based sequential therapy vs clarithromycin based sequential therapy in H-pylori eradication.

Material and methods: It is a randomized clinical trial. Two hundred H. Pylori infected patients diagnosed by rapid urease test (RUT) on UGI endoscopy were randomly divided into two groups A and B. Group B Levofloxacin based sequential regimen and group A clarithromycin based sequential regimen. H-pylori eradication status was evaluated with rapid urease test on UGI endoscopy 6 weeks after completion of sequential therapy.

Results: As per protocol, eradication rates for group B and A were 86% and 81% respectively. Eradication rate for H-pylori is greater with levofloxacin based sequential therapy as compared to that of clarithromycin based sequential therapy but it is not statistically significant $p > 0.05$.

Conclusion: Levofloxacin based sequential therapy has higher eradication rate than clarithromycin based sequential therapy. Although not statistically significant in our study, levofloxacin based sequential therapy could be better alternative for the treatment of H-pylori in areas with high clarithromycin resistance.

Keywords: H-pylori, Levofloxacin, Clarithromycin, Sequential Therapy.

INTRODUCTION

Helicobacter pylori (H-pylori) affect about 50% of world's population and results in various clinical problems. The spectrum of diseases caused by this pathogen ranges from dyspepsia to gastric lymphoma. H-pylori is commonly prevalent in developing countries.¹ Therapy for H-pylori has been a challenge for the treating physician.² H-pylori infections are often chronic, necessitating the use of two or more drugs in its eradication.³ There are numerous regimens recommended for H. pylori eradication which include triple, quadruple or sequential therapy regimens. Currently regimens that use proton-pump inhibitors (PPI,s) in combination with several antibiotics such as clarithromycin, amoxicillin and metronidazole have been highly successful for H. pylori eradication.^{22,23} The sequential therapy was first introduced by Zullo et al in 2000.⁴ Sequential therapy consists of 2 phases in which a proton pump inhibitor

(PPI) and amoxicillin are given for 5 to 7 days and then a PPI, clarithromycin or levofloxacin and metronidazole (or Tinidazole) are given for 5 to 7 days.^{5,6} Initial studies have shown eradication rate of H-Pylori very high with sequential regimen (96%).⁶

Since the resistance to levofloxacin in H-pylori strains is low^{8,9}, the use of levofloxacin instead in the sequential therapy could increase the effectiveness of this regimen.¹⁰

The aim of this study was to compare the efficacy of levofloxacin based sequential therapy and clarithromycin based sequential therapy in H-pylori eradication. Sequential therapy for 14 days may be more effective in eradicating H. pylori as compared with triple therapy in regions where clarithromycin resistance is high and metronidazole resistance is low. In a randomized controlled trial in Taiwan, 900 adults with

H. pylori were assigned to 14-days triple therapy (lansoprazole, amoxicillin, and clarithromycin) or 14-days sequential therapy (lansoprazole and amoxicillin for seven days followed by lansoprazole, clarithromycin, and metronidazole for 7- days) or 10-days sequential therapy (lansoprazole and amoxicillin for five days followed by lansoprazole, clarithromycin, and metronidazole for five days).

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The genome of H-pylori encodes 1500 proteins.¹⁵ Diagnosis of H-pylori is divided into invasive testing i.e biopsy based and non-invasive tests i.e not requires sampling of the gastric mucosa. The standard hematoxylin and eosin (H and E) stain is excellent to determine histologic chronic or chronic active inflammation and demonstrates H-pylori if large number of organisms are present.¹¹⁻¹⁶ Rapid urease test (RUT) is a rapid test for the diagnosis of H-pylori. The RUT is performed at the time of endoscopy. It is based on the principle that urease produced by H-pylori hydrolyses the urea to produce ammonia, leading to increase in the PH of the medium and changes the color of specimen from yellow (negative) to red (positive).

Noninvasive tests include serological tests, urea breath test, stool antigen test. Although Serological tests (IgG antibodies) are generally not useful to confirm the cure, a fall in antibody titers of 20% or more 6 months after completion of therapy may be sensitive in confirming the cure.¹⁷

Cure of H-pylori is not easy and requires combination of antibiotics. The finding that elimination of H-pylori changes the natural history of peptic ulcer disease¹⁸ and gastric mucosa associated lymphoid tissue lymphoma¹⁹ has led to the development of successful strategies to clear the organism from persons with these diseases. This study was designed for evaluating the efficacy of levofloxacin based sequential therapy vs clarithromycin based sequential therapy in H-pylori eradication.

MATERIAL AND METHODS

This prospective clinical study was conducted in department of Gastroenterology and Hepatology, government medical college; Srinagar. All patients who presented as upper gastrointestinal (UGI) bleed i.e hematemesis or melena and dyspepsia were enrolled in the study.

All patients were subjected to UGI endoscopy and biopsies were taken from antrum, corpus and incisura for the diagnosis of H-pylori by RUT. Patients with RUT positive proven H-pylori were enrolled in the study. Patients who presented with UGI bleed, RUT was done on follow of four weeks with one week off PPI, s.

Exclusion criteria

1. History of previous H. pylori eradication therapy.

2. Gastric surgery
3. Pregnancy/lactation
4. Chronic renal failure
5. Decompensated cirrhosis

Intervention: Patients were randomly assigned to one of the therapeutic groups. Eligible patients randomly received one of the therapeutic regimens.

Group A: Clarithromycin based sequential group received: Pantoprazole 40mg twice daily for 7 days
Amoxicillin 1gm twice daily for 7 days
Followed by
Pantoprazole 40mg twice daily for 7 days
Tinidazole 500mg twice daily for 7 days
Clarithromycin 500mg twice daily for 7 days

Group B: Levofloxacin based sequential group received: Pantoprazole 40 mg twice daily for 7 days
Amoxicillin 1gm twice daily for 7 days
Followed by
Pantoprazole 40mg twice daily for 7 days
Tinidazole 500mg twice daily for 7 days
Levofloxacin 250mg twice daily for 7 days
All the participants in the study were re-endoscoped six weeks after the completion of the drug regimen for H-pylori eradication with two weeks off proton pump inhibitors. Test used was RUT in view of non-availability of urea breath test and fecal antigen test at our institution.

STATISTICAL ANALYSIS

Eradication rate was calculated as the percentage of patients whose H-pylori infection was negative at the end of the study. The SPSS 21 statistical software was used for statistical analysis. Statistical analysis of the results was performed using a mean, standard deviation, Chi square test and student's t-test.

RESULTS

The age of 200 patients in our study ranged from 18 to 70 years. The eradication rate in clarithromycin based group is 81% (CI 95%) and eradication rate in levofloxacin based group is 86% (CI 95%). Levofloxacin based sequential group included Men 56 and women 44. Clarithromycin

Presentation	Clarithromycin based (Group A)		levofloxacin Based (Group B)		AB
	n	%	n	%	
Dyspepsia	66	66	66	66	1.000 (NS)
Malena	29	29	26	26	0.636 (NS)
Hematemesis	12	12	13	13	0.831 (NS)

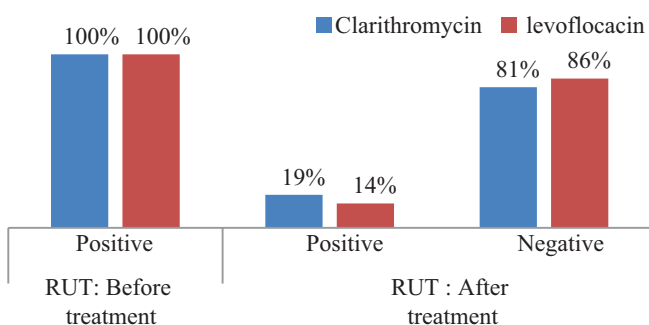
Table-1: Presentation

Endoscopic Findings	Clarithromycin Based (Group A)		Levofloxacin Based (Group B)	
	n	%	n	%
Duodenal Ulcer	19	19	21	21
Gastric Ulcer	11	11	4	4
Corpus predominant gastropathy	53	53	57	57
Antral predominant gastropathy	17	17	18	18

Table-2: Endoscopic findings

		Clarithromycin Based (Group A)		Levofloxacin Based (Group B)		
Rapid urease test		n	%	n	%	BC
Before treatment	Positive	100	100	100	100	1.000 (NS)
After treatment	Positive	19	19	14	14	0.342 (NS)
	Negative	81	81	86	86	
Interpretation success		81	81	86	86	0.342 (NS)

Table-3: Treatment outcome



Graph-1: Treatment outcome

based sequential group included Men 59 and women 41. In clarithromycin based study group the mean age of the patients was 45.4±14.4 and in levofloxacin based sequential therapy the mean age was 44.1±16.1 years. In our study we have found that the eradication rate with levofloxacin based sequential therapy is greater than that of clarithromycin based sequential therapy but it is not statistically significant (p >0.05). Dyspepsia was most common indication for endoscopy – table 1. The most common presentation of patients in our study is dyspepsia (66%). The most common endoscopic finding in our study is antral gastritis- table 2 (53% in group A and 57% in group B).

This randomized clinical trial showed that the eradication rate for H-pylori with levofloxacin based sequential therapy exceeds the eradication rate with clarithromycin based sequential therapy (table-3, graph-1). Eradication rate with levofloxacin and clarithromycin based sequential therapy is 86% and 81% respectively. Given the increasing resistance to antibiotics in H-pylori especially against clarithromycin and decrease in the H-pylori eradication with classic triple therapy, there became an increased demand for a safe and more effective regimens.^{2,8} Sequential therapy includes PPI plus Amoxicillin for 5 to 7 days followed by PPIs, clarithromycin and metronidazole (or Tinidazole) for 5to7 days.⁴ H-pylori eradication rates with classical sequential therapy initially was 95%.^{4,5} One of the recent study have shown a decreased response rate with classic therapy for H-pylori.¹⁴ The results of our study indicate that eradication rate with levofloxacin based sequential therapy exceeds the eradication rate with clarithromycin based sequential therapy.

Only few studies have compared the levofloxacin and clarithromycin based sequential therapy for H-pylori eradication. In Italy trial comparing the levofloxacin and clarithromycin based sequential therapies has shown higher eradication rate with levofloxacin based sequential therapy (95%) as compared to that of clarithromycin based sequential

therapy(80.8%).¹⁴ Another trial conducted in Spain has shown eradication rates of 82.5% and 76.5% with levofloxacin and clarithromycin based sequential therapy respectively.¹³ A recent study by Mosayeb Moradniani has shown that the eradication rates of levofloxacin and clarithromycin based sequential therapy were 87.6% and 76% respectively.²⁹

The main reason for greater effectiveness of levofloxacin based therapy may be low rate of resistance to levofloxacin than clarithromycin.^{12,13,16} The results of our study are consistent with other studies. This can be explained by the fact that there may be low prevalence of levofloxacin resistant strains of H-pylori in our community as well. However this needs further confirmation.

Thus levofloxacin based sequential therapy may be used in the areas where H-pylori are known to have high level of resistance to clarithromycin. Several combination therapies have been effective in the treatment, however resistance rates have been rising and eradication failures have increased to 1 in 5 patients.²⁰ Reported clarithromycin resistance is 10 to 12% in patients infected with H-pylori and that of metronidazole is 25.1% during the period from 1999 through 2002.²¹

CONCLUSION

Sequential therapy was introduced for eradication of H-pylori and had become standard of care in its management. In sequential therapy, levofloxacin based sequential therapy has higher eradication rate as compared to that of clarithromycin based sequential therapy. So in areas of high clarithromycin resistance, it is better to use levofloxacin based sequential therapy.

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