

# Evaluation Efficacy of Clarithromycin and Levofloxacin in the Eradication of Helicobacter Pylori (H.P) Infected Iraqi Patients at Al-Yarmouk Teaching Hospital

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## Abstract

Helicobacter pylori (H.P) infection is an increasing concern in modern medicine due to its effect on the pathogenesis and management of peptic ulcer disease and gastritis and its possible link to gastric adenocarcinoma cases. The eradication of HP is a mandatory approach in documented cases of HP infection mainly gastric and duodenal ulcers. The treatment options is variable globally according to microbial susceptibility test and local guidelines. This study focused on two main options in the eradication of HP and found that levofloxacin based therapy is superior to clarithromycin based approach in the rate of eradication , with comparable rate of adverse events.

**Key words:** *Helicobacter pylori (H.P), Gastritis, Peptic ulcer, Urea breath test, Stool antigen, Clarithromycin, Levofloxacin*

## Introduction

In world about 50% of population , who have Helicobacter pylori (HP) that colonizing in , probably for life unless eradicated by anti-HP treatment. Colonization of HP concert main risk factor of peptic ulcer disease, also gastric mucosa associated lymphoid tissue (MALT) lymphoma gastric adenocarcinoma . Eradication of HP has revolutionized the treatment of peptic ulcer disease, and Treatment is permanent in most cases afterwards. Anti-HP therapy also represents first-line management for low-grade gastric MALT lymphoma cases. Treatment of HP is not recommended as a line of treatment of gastric adenocarcinoma, but preventing HP colonization or eradication may prevent gastric malignancy. In same time , increasing evidence suggests that lifetime HP colonization may give some protective effect against esophageal adenocarcinoma.

In most parts of the United States , prevalence of HP among adults is less than 30% , whilst in developed countries more than 80% (1). Humans are the only host of HP. Children may acquire the HP from their parents or their primary caregiver or other children essentially . Transport usually occurs either through the oral - stool or the oral-oral pathway , but HP is easily cultured from

vomit us and gastroesophageal reflux fluid and to a lesser extent from stool (2,3)

Most of colonized people are healthy and asymptomatic, and only a fraction develop HP related illnesses. About 90% of patients with duodenal ulcers and 70% of gastric ulcer are infected with HP. The distribution and severity of HP-induced gastritis determine the future outcome. In most colonized patients, HP causes a mild pangastritis with little effect on stomach acidity environment and the majority develop no significant clinical outcomes.

In a minority , the infection causes an antral-predominant gastritis characterized by hypergastrinaemia and overt acid production by parietal cells and may end with duodenal ulceration. In a much smaller number of infected people(4), HP causes a corpus-predominant gastritis resulting in atrophy of the gastric mucosa and hypochlorhydria. The hypochlorhydria allows other bacteria to proliferate in the stomach; these other bacteria will result in chronic inflammation and produce mutagenic nitrites from dietary nitrates, predisposing to the development of gastric malignancies. The ulcer probably result as an end point of impaired mucosal defense resulting from a combination of HP infection;

smoking and NSAIDs , rather than highly acidic environment(4)

#### Patient and methods

This study was a single center open label randomized clinical trial to compare the efficacy of levofloxacin versus clarithromycin in the eradication of HP infection.

This study was a randomized, open- label randomized clinical trial to compare the efficacy of both clarithromycin and levofloxacin in the elimination of HP infection.

The study conducted in the outpatient internal medicine clinic at Al-Yarmouk teaching hospital during period (January 2018- January 2019 ) involving 130 patient, In clarithromycin group two patients was lost to follow-up and excluded and in the levofloxacin group, three patients were lost to follow-up and thus, were excluded, so the study actually covered 125 patient (52 female and 73 male) , age patients from (19 to 59)years old.

Consent had been explained and obtained from the patients under supervision of ethical committee at Department of medicine at Al-Yarmouk teaching hospital.

Inclusion criteria for this study were as follows: diagnose patients have HP infection depending on history and clinical examination then confirmed by either stool antigen detection of HP or urea breath test or endoscopy and histopathology analysis.

Exclusion criteria for this study were as follows: pregnancy, previous use of clarithromycin and levofloxacin in the preceding month, consumption of alcohol or substancemisuse ; advanced chronic gastrointestinal disease cirrhosis, gastric cancer, inflammatory bowel disease , cerebrovascular accidents , advance renal insufficiency, advance heart failure and severe debilitating illnesses.

Then the patient had been distributed randomly to be treated with either Clarithromycin based therapy (clarithromycin 500mg twice daily , metronidazole (500mg)twice daily and lansoprazol (30mg)twice ) or Levofloxacin based therapy (levofloxacin (500mg) twice daily , metronidazole (500mg)twice daily, and lansoprazole (30mg)twice daily ) for a period between 10-14 days.

In this study we decided to replace amoxicillin; which is usually given with levofloxacin, with metronidazole in levofloxacin group for both reasons:

1- High rate of allergy to penicillins in Iraqi society.

2-Combination of metronidazole with levofloxacin is a new strategy to be evaluated for the future newer combinations in eradication of Hp.

At the end point (2) groups were compared with respect to proportion of HP eradication with either stool antigen or urea breathe test 45 days or more thereafter , then the results had been documented .

Any significant side effect of therapy had been documented and the patient followed up for any serious adverse events , discontinuation , or drug non compliance.

#### Diagnosis

The current options available for diagnosis of HP infection are listed below:

- Invasive:

1- Biopsy urease test

2-histopathology

3-Microbial culture

- Non Invasive:

1-Serology

2-Urea breath test

3-Stool antigen testing

Breath tests or faecal antigen tests are best because of simplicity ; accuracy and non-invasion (4)

#### Statistical Analysis

Analysis of data was carried out using the available statistical package of SPSS-25 . significance of difference of different percentages (qualitative data) were tested using Chi-square test ( $\chi^2$ -test) with application of Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the P value was equal or less than 0.05

## Finding

Current regimens consist of a Proton pump inhibitors (PPI) and ( 2 or 3) antimicrobial agents were given for (10–14) days (Table-1). The optimal regimens vary geographically, depending on the known rates of

primary antibiotic resistance in most *H. pylori* strains locally, therefore, guidelines on optimal regimens for HP eradication in individual countries are evolving, and physicians should select the most up-to-date local guideline.

**Table (1): Commonly Recommendation Treatment systems for H.Pylori**

Regimen (Duration in days )	DRUG 1	DRUG2	DRUG3	DRUG4
Regimen 1 (10- 14 )	Lansoprazole(30)mg bid	Clarithromycin (500) mg bid	Metronidazole (500) mg bid	-
Regimen 2 (10- 14 )	Lansoprazole (30)mg bid	Clarithromycin (500) mg bid	Amoxicillin (1g) bid	-
Regimen 3 (10- 14 )	Lansoprazole (30)mg bid	Bismuth subsalicylate (2) tabs qid	TetracyclineHCl (500)mg qid	Metronidazole (500) mg tid
Regimen 4 : concomitant 14 days	Lansoprazole (30)mg bid	Amoxicillin (1)g. bid	Clarithromycin (500)mg bid	Tinidazole (500)mg bid
Regimen 5 :10 days	Lansoprazole (30)mg bid	Amoxicillin (1) g bid	Levofloxacin (500) mg bid	-

Two elements as most important in successful HP eradication is the patient's commitment to the system and the use of drugs that the patient's HP strain has not acquired.

Increasing levels of primary HP resistance to clarithromycin, levofloxacin are of growing concern(5). In most parts of the world (the main exception being northwestern Europe), the rate of primary clarithromycin resistance is high enough that regimens containing only clarithromycin plus one antibiotic often fail; regimens with clarithromycin and two other antibiotics remain superior as the other two antibiotics are likely to eradicate HP even if the strain is resistant to clarithromycin. When a patient is known to have been exposed—even distantly—to clarithromycin or levofloxacin, these two drugs should be avoided. Resistance to amoxicillin or tetracycline is unusual, even if these antibiotics have been given previously, and metronidazole resistance is only partial; thus there is no need to avoid using these antibiotics even if they have been previously used. Assessment of antibiotic susceptibilities before

treatment is not usually done because endoscopy and mucus biopsy are necessary to obtain HP culture and because most microbiological laboratories lack experience in HP culture. If initial anti HP treatment fails, the usual approach is re-treatment with another antibiotic regimen (table-1).

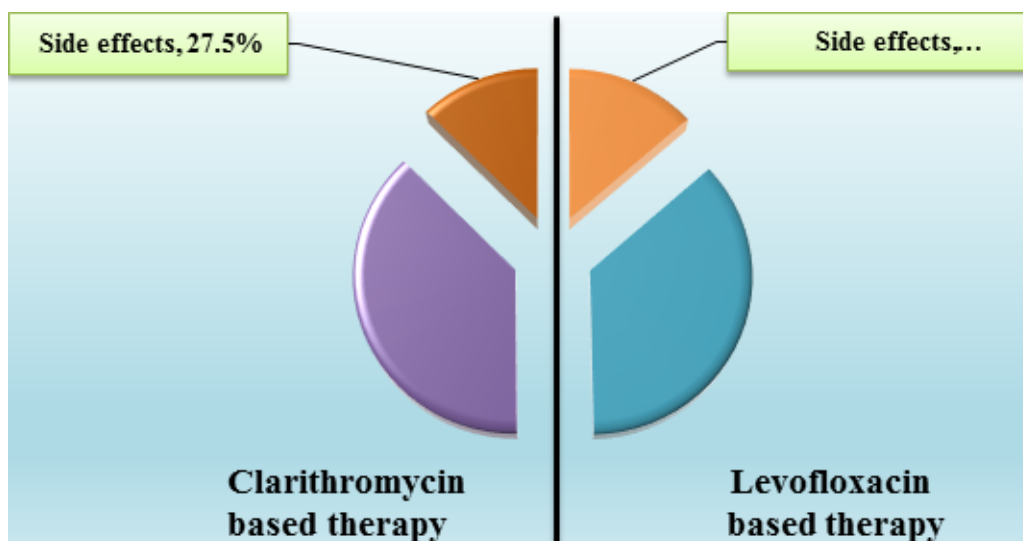
The third-line ideally should include endoscopy; biopsy; culture as well as treatment based on antibiotic sensitivity. However, empirical third-line therapies can be applied(6)

From the total 69 patients who had been treated with Clarithromycin based therapy only 34 patient (49%) respond and failure rate is approximately (51%) 35 patients. While those who had been treated Levofloxacin based therapy 56 patients; 40 patients (71%) had respond, while failure rate is about (29%) 16 patients (table- 2).

**Table (2): Compare regarding success rate of therapy**

Clarithromycin based: 69(55%)		Levofloxacin based: 56(45%)	
Respond	Failure	Respond	Failure
34 (49%)	35 (51%)	40 (71%)	16 (29%)
Total patient number : 125			

For Response; P=0.012\* Significant difference in proportions using Pearson Chi-square test at 0.05 level



**Figure (1):Incidence of anti HP therapy adverse effects.**

Incidence of minor adverse effect in both therapies is also reported 19 cases (27.5%) in clarithromycin group and 14 cases (25%) in levofloxacin group. Diarrhea is the most documented side effect of therapy in both groups which happens in 8 cases of clarithromycin based therapy and 5 cases of levofloxacin lines, metallic taste also reported frequently but it may be due to metronidazole mainly other adverse effects had been reported in lower incidence rate but non of them resulted in discontinuation of therapy (table- 3).

**Table (3): Adverse events of anti HP treatment in both study groups**

Study group			
Clarithromycin based group		Levofloxacin based group	
Diarrhea	8 (11.6%)		5 (8.9%)
Metallic taste	7 (10%)		6 (10.7%)
Nausea	3 (4.3%)		3 (5.3%)
Vomiting	5 (7.2%)		1 (1.8%)
Constipation	2(2.8%)		0 (0%)
Headache	3 (4.3%)		0 (0%)
Abdominal discomfort	2 (2.8%)		4 (7.1%)
Skin rash	1 (1.4%)		0 (0%)
Total	19 (27.5%)*		14 (25%)*

\*some cases develop more than one adverse events in the same time so the total is not necessarily equal the sum of total number of patients who develop adverse events in both groups.

## Discussion

There were several findings in this study starting with comparing the efficacy of both line of management, there is significant difference in efficacy favoring levofloxacin based therapy as compared with clarithromycin which carry high failure rate exceeding 50% based line (P value 0.012). Also current study disclose that the rate of incidence of significant therapy adverse effect is almost equal in both lines; 25% for levofloxacin based therapy versus 27.5% for clarithromycin based therapy (P value 0.90).

If we compare that with the previous Iranian study regarding Comparison efficacy of both clarithromycin and levofloxacin in the eradication of Hp infection, levofloxacin-based therapy is preferable to clarithromycin-based regimen in HP eradication which achieved higher optimal rate of eradication less than 80% success rate (7), so the result of this study is almost comparable in which 71% was the success rate of levofloxacin group and 49% success rate in clarithromycin group compared with 80.4 and 57.4% for levofloxacin and clarithromycin group respectively (7).

This result may reflect the higher incidence of clarithromycin resistant strains in the population and that finding should be supported in the future by more extensive workup involving upper endoscopy and sampling for the microbiological evaluation (culture and antimicrobial sensitivity testing) or molecular based diagnostic assay for resistance detection. The incidence of adverse events with treatment had been reported in 19 cases with clarithromycin group and 14 in levofloxacin group but none of the resulted in termination of therapy but may result in discomfort and anxiety to the patient because most of these adverse events involve gastrointestinal system which is the host of HP.

We have to point that this study is a clinical trial depend mainly on the clinical response to therapy and the confirmation of eradication of HP with breath test or stool antigen, so it didn't include microbiological antimicrobial sensitivity test so it didn't necessarily suggest the real spectrum of bacterial resistance. Also the study is a single center study and more wide multicenter trial is needed for more clarification of the real incidence of HP clarithromycin resistance in the population.

**Conclusions:** Levofloxacin based therapy is superior to clarithromycin based therapy in eradication of HP infection. Both lines have comparable incidence of

adverse events.

**Recommendations:** We recommend to depend on levofloxacin based triple therapy at least first alternative option if first line fails in eradication of HP cases in Iraq as it is effective, with accepted adverse events profile. Also we recommend against the use of clarithromycin based therapy in the management in new cases of HP infection due to high failure rate. Thorough antimicrobial sensitivity evaluation of emerging HP strains should be considered for determining local anti HP treatment guidelines.

**Conflict of Interest:** None

**Source of Findings:** Self

**Ethical Clearance:** None

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