Original Article

The Comparison of Levofloxacin- and Clarithromycin-Based Bismuth Quadruple Therapy Regimens in *Helicobacter pylori* Eradication

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Abstract

Objective: The aim of the current study was to compare the efficacy of quadruple therapy including levofloxacin and clarithromycin for *Helicobacter pylori* eradication. **Methods:** This clinical trial study was conducted on 189 patients with *H. pylori* infection who underwent gastroscopy and stomach biopsy in Shahid Beheshti Hospital, Kashan, Iran. After classification of patients, one group was treated with bismuth subcitrate (120 mg, 2 tablet/12 h), omeprazole (20 mg/12 h), amoxicillin (1 g/12 h), and clarithromycin (500 mg/12 h) and other group with bismuth subcitrate (120 mg, 2 tablet/12 h), omeprazole (20 mg/12h), amoxicillin (1 g/12 h), and levofloxacin (500 mg/12 h) for 2 weeks. After the end of the antibiotic treatment, omeprazole therapy was continued for 4 weeks. Two weeks after discontinuation of omeprazole, fecal antigen test was performed for both the groups to confirm the eradication of *H. pylori* infection. **Findings:** The success of *H. pylori* eradication in the levofloxacin and clarithromycin groups was observed in 78 (89.7%) and 71 (69.6%) patients, respectively ($P < 0.01$). A significant difference was also seen between the two groups in terms of side effects and its incidence ($P < 0.01$), so that the incidence of side effect types in the clarithromycin group was more than the levofloxacin group except muscular pain and fatigue ($P < 0.01$). **Conclusion:** Levofloxacin-based quadruple regimen therapy was superior to clarithromycin-based quadruple regimens regarding *H. pylori* eradication and side effects. Therefore, the levofloxacin-based regimen can be considered as an effective treatment for the first-line anti-*H. pylori* therapy.

Keywords: *Clarithromycin therapy, Helicobacter pylori infection, Levofloxacin*

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Introduction

Helicobacter pylori is a prevalent, chronic, and worldwide infection.[1] In general, the prevalence of this infection in developing countries is higher than in developed countries.[2] Moreover, the prevalence of *H. pylori* infection is different in various countries and geographic areas in Asia,[2,3] so that the prevalence rate is 31% in Singapore, 39% in Japan, 58% in China, 75% in Vietnam, and 58.% in China.[4] The rate of *H. pylori* infection in a diverse area of Iran is different, so that the prevalence in Kurdistan is 36% and in Ardabil 90%.[5-7] *H. pylori* infection is associated with gastrointestinal diseases such as gastric inflammation, peptic ulcer, and gastric mucosa-associated lymphoid tissue lymphoma.[4] It is the strongest known risk factor for gastric cancer which is the second leading cause of cancer-related death worldwide.[8]

The role of *H. pylori* infection in functional dyspepsia is controversial.[9,10] Eradicating *H. pylori* prevents the recurrence of disease, decreases the risk of gastric cancer, prevents the spread of *H. pylori* infection, and decreases the cost of gastric cancer treatment.[3]

A major issue in anti-*H. pylori* treatment is antibiotic resistance,[10] so that *H. pylori* resistant to antibiotics

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has attained an alarming level worldwide, which has a main effect on treatment efficacy.[11] Clarithromycin resistance in Iran has increased from 1.4% in 1997 to 26.5% in 2013.[3] The current treatment relies on a combination of antimicrobial agents including levofloxacin, clarithromycin, metronidazole, and amoxicillin and acid suppressant agents such as proton-pump inhibitors. Recently, clarithromycin-based regimens are considered as standard triple therapies. However, clarithromycin resistance has been seen in some studies. Clarithromycin resistance is associated with one of the three-point mutations in the 23S rRNA gene of *H. pylori*. These mutations are associated with more than 90% of clarithromycin resistance in developed countries.[12] Recent research showed higher efficacy of levofloxacin-based regimens as first-line triple therapy for the eradication of *H. pylori* eradication.[13-20] Moreover, because of the high prevalence of *H. pylori* infection in Iran and increasing resistance of pathogen to medications, evaluation of novel therapeutic alternatives is necessary. Moreover, few studies have assessed levofloxacin- and clarithromycin-based bismuth quadruple therapy regimens in *H. pylori* eradication in Iran. Therefore, the aim of the current study was to compare the efficacy of quadruple levofloxacin- versus clarithromycin-based therapy in the treatment of *H. pylori* infection.[21]

Methods

This randomized clinical trial study was conducted on 189 patients with *H. pylori* infection who referred with dyspepsia complaint to the gastroenterology clinic and internal wards of Shahid Beheshti Hospital of Kashan, Iran, during 2019, and *H. pylori* infection was approved in them after gastroscopy, stomach biopsy, or fecal antigen test (specificity and sensitivity of gastroscopy and stomach biopsy is similar). Figure 1 shows the CONSORT flow diagram for two groups of patients.

The current study was approved by the Ethical Committee of Kashan University of Medical Sciences and Iranian Registry Clinical Trial (IRCT 20190606043826N1). After taking written consent form, patients with positive *H. pylori* in the age range of 14-70 years were entered into the study and also excluded those with documented chronic liver, kidney, a nd gastrointestinal diseases, pregnancy, breast feeding, current use of antibiotics like macrolide, patients with the treatment of *H. pylori* in recent month, pregnant and lactating women, and patients with documented chronic liver, kidney, and gastrointestinal diseases were considered as exclusion criteria.

Information including age, gender, and complications were extracted from medical records. Then, these

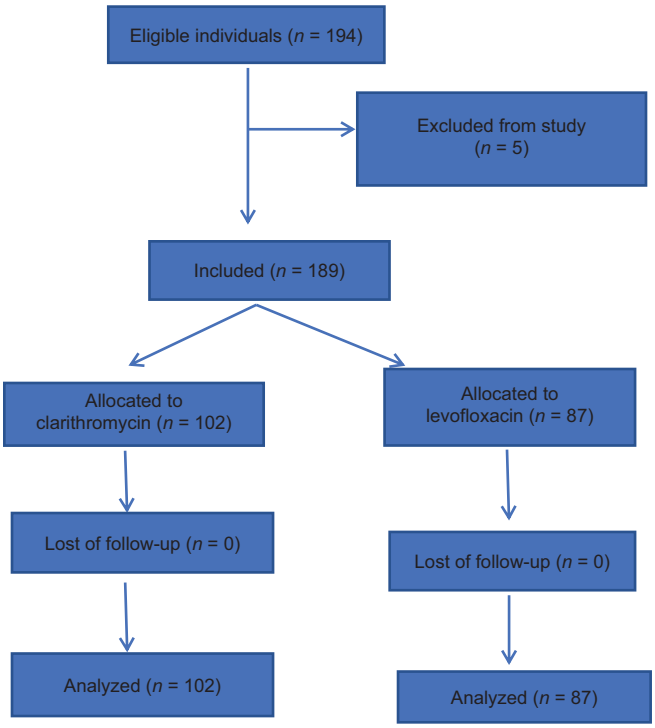

Figure 1: CONSORT flow diagram of the study

patients were randomly classified into two groups using simple random sampling. One group of patients was treated with bismuth subcitrate (120 mg, 2 tablet/12 h), omeprazole (20 mg/12 h), amoxicillin (1 g/12 h), and clarithromycin (500 mg/12 h) and other group was treated with bismuth subcitrate (120 mg, 2 tablet/12 h), omeprazole (20 mg/12 h), amoxicillin (1 g/12 h), and levofloxacin (500 mg/12 h) for 2 weeks. After the end of the antibiotic treatment, omeprazole treatment was continued for 4 weeks. Two weeks after discontinuation of omeprazole, fecal antigen test (Astra Company, Italy) was performed for both the groups to confirm the primary diagnosis and eradication of *H. pylori* infection. High availability and cost-effective are the advantages of this method.

Data were entered into SPSS version 19 (IBM Corporation, New York, USA). Fisher's exact test and Chi-square test were used for the analysis of data. $P < 0.05$ was considered statistically significant.

Results

Current study was conducted on patients with *H pylori* infection to compare the effect of levofloxacin and clarithromycin in treatment of *H pylori* eradication .among 189 patients, 102 patients (53.9%) were male and 87 (46.0%) were female. One hundred and two patients were treated with clarithromycin and eighty-seven patients treated with levofloxacin. Five patients (3 patients in the levofloxacin group and 2 in

the clarithromycin group) were excluded from the study due to intolerance to drug side effects. At the end of the 1st and 2nd weeks of treatment, patients were evaluated for proper drug use and drug side effects. Then, all of them were recorded in a questionnaire.

Comparison of patients in terms of age in the two groups showed that the mean age of patients in the clarithromycin and levofloxacin groups was 46.33 ± 13.57 and 44.62 ± 12.30, respectively ($P = 0.368$).

Moreover, there was a significant difference between the two groups regarding the eradication rate of *H. pylori* ($P < 0.01$), so that the eradication of *H. pylori* in the levofloxacin group was more than in the clarithromycin group.

Table 1 shows a comparison of patients in terms of sex, eradication of *H. pylori* medical side effects, and incidence of its side effects.

As shown in Table 1, a significant difference was seen between the two groups of patients in terms of side effects and its incidence ($P < 0.01$). In this regard, the incidence of side effects including bitter taste in the mouth and nausea in the clarithromycin group was more than the levofloxacin group. However, muscular pain and fatigue in the levofloxacin group were more than the clarithromycin group ($P < 0.01$).

Discussion

According to the results of the current study, the eradication rate of *H. pylori* in the levofloxacin group was more than that of in the clarithromycin group. Haji-Aghamohammadi *et al*. compared the efficacy of clarithromycin- versus levofloxacin-based regimen in the eradication of *H. pylori* infection. The findings showed that *H. pylori* eradication was successful in 75% of the patients in the case group and 51.7% of them in the control group. Therefore, it seems that levofloxacin therapy has better efficacy than clarithromycin regarding *H. pylori* eradication.[20] One study was conducted in China for the evaluation of *H. pylori* infection eradication. The findings showed that the rate of infection eradication for two triple therapies (clarithromycin, amoxicillin, and lansoprazole and levofloxacin, amoxicillin, and lansoprazole) was 66.67% and 94.87%, respectively. It indicated that levofloxacin therapy was more effective than clarithromycin for *H. pylori* infection eradication. These studies confirmed our findings.[21]

Table 1: Comparison of patients in terms of sex, eradication of *Helicobacter pylori*, complication, and incidence of complications in two groups

Parameters	Clarithromycin, *n* (%)	Levofloxacin, *n* (%)	*P*
Sex			0.676
Male	50 (49)	41 (45.9)	
Female	52 (51)	46 (54.1)	
Eradication of *Helicobacter pylori*			0.001
Successful	71 (69.6)	78 (89.7)	
Unsuccessful	31 (30.4)	9 (10.3)	
Side effect type			<0.001
Bitter taste in the mouth	68 (66.7)	0	
Muscular pain	0	13 (14.9)	
Nausea	4 (3.9)	4 (4.6)	
Fatigue	0	2 (2.3)	
No complication	30 (29.4)	68 (78.2)	
Incidence of side effects			<0.001
No	30 (29.4)	68 (78.2)	
Yes	72 (70.6)	19 (21.8)	

Assem *et al*. evaluated the efficacy and safety of esomeprazole, levofloxacin, and clarithromycin regimens for the treatment of *H. pylori* eradication and observed the superiority of the combined levofloxacin and clarithromycin as first-line therapy for *H. pylori* eradication than previous regimens including clarithromycin or levofloxacin plus amoxicillin.[13] Gisbert *et al*., in two separate studies, reported that the eradication rate of *H. pylori* infection for levofloxacin drug is 51.6% and 94.3%, respectively.[22] Gan *et al*. also evaluated two different dosages of levofloxacin including oral levofloxacin (200 mg twice daily) and oral levofloxacin (500 mg once daily) for the treatment of *H. pylori* infection. The results showed the superiority of oral levofloxacin 200 mg twice daily to oral levofloxacin 500 mg once daily for the eradication of *H. pylori* infection.[23] Other studies have recommended 500 mg levofloxacin once daily for *H. pylori* infection eradication.[24] Qian *et al*. in China evaluated levofloxacin-containing triple therapy (levofloxacin, 500 mg, once daily, amoxicillin 1 g twice daily, and esomeprazole 20 mg twice daily) as the first-line treatment for *H. pylori* eradication.[25] Therefore, the recommended dosage of levofloxacin is 500 mg once daily or 200 mg twice daily.

In addition, studies from East Asia showed a lower eradication rate, but studies in Western countries and India showed higher eradication rates.[26-29] It seems that duration of therapy, drug dosage, and ethnicity may be considered as the cause of these differences in various studies.

Cheha *et al*. assessed the efficacy of two triple therapies (500 mg clarithromycin, 20 mg esomeprazole, and 1000 mg amoxicillin and 500 mg levofloxacin, 20 mg esomeprazole, and 1000 mg amoxicillin on the eradication of *H. pylori* infection. The findings showed

that clarithromycin has a more eradication rate of *H. pylori* than that levofloxacin, but both medications have low effectiveness for eradication rates. The result of this study was inconsistent with our study. Medications used in Cheha *et al*. study are locally manufactured. Therefore, it seems that the reason of difference between the two studies may be due to drug type.[30]

In our study, drug adverse effects were seen in 21.8% of the patients in the levofloxacin group and 70.6% in the clarithromycin group. Haji-Aghamohammadi *et al*. reported that drug side effects were observed in 8.5% of the patients in the levofloxacin group and 12.5% in the clarithromycin group.[20] Therefore, it seems that levofloxacin is safer than clarithromycin; however, the higher cost of levofloxacin causes that the use of levofloxacin is not considered as the first line of treatment for *H. pylori* infection. However, Romano *et al*. evaluated the efficacy of levofloxacin- versus clarithromycin-containing sequential therapy for *H. pylori* eradication. They selected 375 patients with *H. pylori* and were randomly assigned them to the two groups. The results showed that there is no difference in incidence of adverse events and prevalence of antimicrobial resistance which was inconsistent with our study.[31] One of the common drugs used in our study and Romano *et al*. study was bismuth subcitrate. Bismuth has synergistic effects with antibiotics. Moreover, no bacterial resistance was seen against bismuth in *H. pylori*, which causes that bismuth subcitrate can be considered as a preferred antimicrobial agent for the eradication of *H. pylori*.[32,33]

According to the result of the current study, levofloxacin-based quadruple regimen therapy was superior to clarithromycin-based quadruple regimens. Therefore, the levofloxacin-based regimen can be considered as an effective treatment for the first-line anti-*H. pylori* therapy.

The major limitations of this study were lack of data about possible clinical manifestations of *H. pylori* infection after treatment in the two groups and lack of data about clarithromycin and levofloxacin resistance pattern of *H. pylori* isolates in the cohort.

Authors' Contribution

Abbas Arj contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. Marzieh mollaei contributed to the conception and design of the work, conducting the study, approval of the final version of the manuscript and agreed for all aspects of the work. Mohsen Razavizade contributed in the design of the work, contrib uted in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. Alireza moraveji contributed to the design of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. Allauthors contributed the idea of research, design of study, data analysis and manuscript preparation.

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Conflicts of interest

There are no conflicts of interest.

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