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/12 h), 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
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 Beheshhti 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, and 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 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]

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

---

### 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|                       |                     |       |
| Successful                        | 71 (69.6)             | 78 (89.7)           | 0.001 |
| 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)           |       |
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.[30] 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, 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. 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. All authors contributed the idea of research, design of study, data analysis and manuscript preparation.

**Acknowledgments**
The authors would like to thank the staff of Shahid Beheshti Hospital, Kashan, Iran, for their support, cooperation, and assistance throughout the period of study.

**Financial support and sponsorship**
Nil.

**Conflicts of interest**
There are no conflicts of interest.

**REFERENCES**

1. Alahdab YO, Kalayci C. *Helicobacter pylori*: Management in 2013. World J Gastroenterol 2014;20:5302-7.

2. Fock KM, Ang TL. Epidemiology of *Helicobacter pylori* infection and gastric cancer in Asia. J Gastroenterol Hepatol 2010;25:479-86.

3. Mitulahussurur M, Yamaoka Y. Population-Based Strategies for *Helicobacter pylori*-Associated Disease Management: Asian Perspective. *H. pylori* Research; 2016. p. 519-42.

4. Yang JC, Lu CW, Lin CJ. Treatment of *Helicobacter pylori* infection: Current status and future concepts. World J Gastroenterol 2014;20:5283-93.

5. Fakheri H, Saberi Firoozi M, Bari Z. Eradication of *Helicobacter pylori* in Iran: A review. Middle East J Dig Dis 2018;10:5-17.

6. Moosazadeh M, Lankarani KB, Ashari M. Meta-analysis of the prevalence of *Helicobacter pylori* infection among children and adults of Iran. Int J Prev Med 2016;7:48.

7. Malekzadeh R, Sotoudeh M, Derakhshan MH, Mikhaili J, Yazdianbod A, Merat S, *et al.* Prevalence of gastric precancerous lesions in Ardabil, a high incidence province for gastric adenocarcinoma in the Northwest of Iran. J Clin Pathol 2004;57:37-42.

8. Wrobleski LE, Peek RM Jr, Wilson KT. *Helicobacter pylori* and gastric cancer: Factors that modulate disease risk. Clin Microbiol Rev 2010;23:713-39.

9. Zullo A, Hassan C, De Francesco V, Repici A, Manta R, Tomao S, *et al.* *Helicobacter pylori* and functional dyspepsia: An unsolved issue? World J Gastroenterol 2014;20:8957-63.

10. Hosseini E, Pourina F, de Wiele TV, Safaei HG, Adibi P. *Helicobacter pylori* in Iran: A systematic review on the association of genotypes and gastroduodenal diseases. J Res Med Sci 2012;17:280-92.

11. Savoldi A, Carrara E, Graham DY, Conti M, Tacconelli E. Prevalence of antibiotic resistance in *Helicobacter pylori*: A systematic review and meta-analysis in World Health Organization Regions. Gastroenterology 2018;155:1372-382E20.

12. Mégraud F, Lehours P. *Helicobacter pylori* detection and antimicrobial susceptibility testing. Clin Microbiol Rev 2007;20:280-322.
Arj, et al.: Levofloxacin and clarithromycin based regimens in Helicobacter pylori eradication

13. Assem M, El Azab G, Rasheed MA, Abdelfatah M, Shastery M. Efficacy and safety of levofloxacin, clarithromycin and esomeprazole as first line triple therapy for Helicobacter pylori eradication in Middle East. Prospective, randomized, blind, comparative, multicenter study. Eur J Intern Med 2010;21:310-4.

14. Cammarota G, Cianci R, Cannizzaro O, Cucco L, Pirozzi G, Gasbarrini A, et al. Efficacy of two one-week rabeprazole/levofloxacin-based triple therapies for Helicobacter pylori infection. Aliment Pharmacol Ther 2000;14:1339-43.

15. Antos D, Schneider-Brachert W, Bästlein E, Hänel C, Haferland C, Buchner M, et al. 7-day triple therapy of Helicobacter pylori infection with levofloxacin, amoxicillin, and high-dose esomeprazole in patients with known antimicrobial sensitivity. Helicobacter 2006;11:39-45.

16. Marzio L, Coraggio D, Capodicasa S, Grossi L, Cappello G. Role of the preliminary susceptibility testing for initial and after failed therapy of Helicobacter pylori infection with levofloxacin, amoxicillin, and esomeprazole. Helicobacter 2006;11:237-42.

17. Nista EC, Candelli M, Zocco MA, Cremonini F, Ojetti V, Finizio R, et al. Levofloxacin-based triple therapy in first-line treatment for Helicobacter pylori eradication. Am J Gastroenterol 2006;101:1985-90.

18. Gisbert JP, Fernández-Bermejo M, Molina-Infante J, Pérez-Gallardo B, Prieto-Bermejo AB, Mateos-Rodríguez JM, et al. First-line triple therapy with levofloxacin for Helicobacter pylori eradication. Aliment Pharmacol Ther 2007;26:495-500.

19. Gisbert JP, Bermejo MF, Infante JM, Gallardo BP, Bermejo AB, Rodriguez JM, et al. Levofloxacin, amoxicillin, and omeprazole as first-line triple therapy for Helicobacter pylori eradication. J Clin Gastroenterol 2009;43:384-5.

20. Haji-Aghamohammadi AA, Bastani A, Miroliace A, Oveis S, Safarnezhad S. Comparison of levofloxacin versus clarithromycin efficacy in the eradication of Helicobacter pylori infection. Caspian J Intern Med 2016;7:267-71.

21. Cheng H, Hu FL, Zhang GX, Shi RH, Du YQ, Li ZS, et al. Levofloxacin-based triple therapy for first-line Helicobacter pylori eradication treatment: A multi-central, randomized, controlled clinical study. Zhonghua Yi Xue Za Zhi 2010;90:79-82.

22. Gisbert JP, Gonzalez L, Calvet X. Systematic review and meta-analysis: Proton pump inhibitor vs. Ranitidine bismuth citrate plus two antibiotics in Helicobacter pylori eradication. Helicobacter 2005;10:157-71.

23. Gan HY, Peng TL, Huang YM, Su KH, Zhao LL, Yao LY, et al. Efficacy of two different dosages of levofloxacin in curing Helicobacter pylori infection: A prospective, single-center, randomized clinical trial. Sci Rep 2018;8:9045.

24. Qian J, Ye F, Zhang J, Yang YM, Tu HM, Jiang Q, et al. Levofloxacin-containing triple and sequential therapy or standard sequential therapy as the first line treatment for Helicobacter pylori eradication in China. Helicobacter 2012;17:478-85.

25. Chinese Society of Gastroenterology, Chinese Study Group on Helicobacter pylori, Liu WZ, Xie Y, Cheng H, Lu NH, Hu FL, et al. Fourth Chinese National Consensus Report on the management of Helicobacter pylori infection. J Dig Dis 2013;14:211-21.

26. Dib J Jr, Alvarez B, Mendez L, Cruz ME. Efficacy of PPI, levofloxacin and amoxicillin in the eradication of Helicobacter pylori compared to conventional triple therapy at a Venezuelan hospital. Arab J Gastroenterol 2013;14:123-5.

27. Gisbert JP. Rescue therapy for Helicobacter pylori infection 2012. Gastroenterol Res Pract 2012;2012:94-97.

28. Gisbert JP, Morena F. Systematic review and meta-analysis: Levofloxacin-based rescue regimens after Helicobacter pylori treatment failure. Aliment Pharmacol Ther 2006;23:35-44.

29. Gopal R, Elamurugan TP, Kate V, Jagdish S, Basu D. Standard triple versus levofloxacin based regimen for eradication of Helicobacter pylori. World J Gastrointest Pharmacol Ther 2013;4:23-7.

30. Cheha KM, Ali Dib SO, Alhalabi MM. Comparing efficacy of 14-day triple therapy clarithromycin versus levofloxacin on eradication of H pylori infection in Syrian population. Clinical Trials.gov 2016;8:14-7.

31. Romano M, Cuomo A, Gravina AG, Miranda A, Iovene MR, Tiso A, et al. Empirical levofloxacin-containing versus clarithromycin-containing sequential therapy for Helicobacter pylori eradication: A randomised trial. Gut 2010;59:1465-70.

32. Malfittheiner P, Megraud F, O’Morain CA, Gisbert JP, Keipers EJ, Axon AT, et al. Management of Helicobacter pylori infection-the maastricht V/florence consensus report. Gut 2017;66:6-30.

33. Chiba N. Effects of in vitro antibiotic resistance on treatment: Bismuth-containing regimens. Can J Gastroenterol 2000;14:885-9.

34. Cheha KM, Ali Dib SO, Alhalabi MM. Comparing efficacy of 14-day triple therapy clarithromycin versus levofloxacin on eradication of H pylori infection in Syrian population. Clinical Trials.gov 2016;8:14-7.