Journal of Kerman University of Medical Sciences
2022; 29(2): 123-133
Original Article
http://jkmu.kmu.ac.ir/

Evaluation of Levofloxacin-containing Regime in Comparison with Clarithromycin-containing Regime in Eradicating *Helicobacter pylori* Infection in Kerman

Bizhan Ahmadi [1], Masoud Hajmohammadi [2], Ali Saeed pour [1], Motahareh Zaherara [3*], Sara Shafieepour[1], Hoshang Ghazizadeh Ahsaei[4]

1. Gastroenterology and Hepatology Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
2. Department of Internal Medicine, School of Medicine, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran
3. Department of Medical Basic Sciences, School of Medicine, Bam University of Medical Sciences, Bam, Iran
4. Sepehr Laboratory, Kerman, Iran

ABSTRACT

Background: *Helicobacter pylori* (*H.pylori*) is the main known cause of gastritis, gastroduodenal ulcer disease, and gastric cancer. Eradication of *H.pylori* can be an effective method of treatment for peptic ulcer disease and mucosa-associated lymphoid tissue lymphoma. This study aimed to compare the effectiveness of levofloxacin versus clarithromycin in the eradication of *H.pylori.*

Methods: This randomized clinical trial was conducted on 170 cases with *H.pylori* infection in Kerman. The participants were randomly allocated to two groups. As the first line therapy, 'A' group was treated twice a day with clarithromycin (500mg), pantoprazole (40mg) and amoxicillin (1gr) for 14 days and 'B' group was treated twice a day with levofloxacin (250mg), pantoprazole (40mg) and amoxicillin (1gr) for 14 days. Stool *H.pylori* antigen test was performed one month after the end of treatment. To analyze the data, descriptive and analytical methods and SPSS software version 22 were used.

Results: The study cases were comprised of 170 individuals (52.35%female). The mean age of patients in 'A' and 'B' groups was 42±11.88 and 41±13.75 years, respectively. *H.pylori* eradication was successful in 61.1% of 'A' group and 92.9% of 'B' group showing a significant difference (P=0.037). Drug complications were reported in 7.1% of 'A' group and 4.7% of 'B' group which showed no significant difference between the two groups (P=0.772). The most common drug complication in both groups was abdominal pain (2.3%).

Conclusion: The results of this study indicated that levofloxacin-containing regimen was more effective in eradicating *H.pylori* than the standard clarithromycin triple therapy.

Keywords: Eradication, *Helicobacter pylori*, Antibiotic, Digestion

Citation: Ahmadi B, Hajmohammadi M, Saeed pour A, Zaherara M, Shafieepour S, Ghazizadeh Ahsaei H. Evaluation of levofloxacin-containing regime in comparison with clarithromycin-containing regime in eradicating *helicobacter pylori* infection in Kerman. Journal of Kerman University of Medical Sciences 2022; 29(2): 123-133. doi:
Received: 02.12. 2021
Accepted: 11.01. 2022
*Correspondence: Motahareh Zaherara; Email: mzaherara@yahoo.com

Published by Kerman University of Medical Sciences

Introduction

Helicobacter pylori (*H. pylori*) is the most common bacterial infection that affects humans globally (1). It attaches to the gastric mucosa (2, 3) and can cause problems such as peptic ulcer disease, gastric malignancy and dyspepsia, gastric cancer and lymphoma of mucosa- associated lymphoid tissue (MALT) that is more prevalent in developing countries (4-10). Approximately 50% of the world population is known to be infected with this infection being more common, up to 80% by the age of 20, in developing countries and with potential increases with aging (11). Epidemiological studies suggest that the prevalence of *Helicobacter pylori* infection in Iran is 90% in people over 35 years of age (12). Contaminated food, water or dishes are the causes. This disease is more common in countries or communities with no proper sanitation or unsafe drinking water (13). Infection with *Helicobacter pylori* is likely acquired through oral ingestion, especially in early childhood. Spontaneous removal of the bacterium is fairly common in children, but infection with *Helicobacter pylori* in adults is generally chronic and does not improve without specific treatment (14). A variety of diagnostic procedures using invasive and non-invasive techniques are developed to detect *H. pylori* infection. Invasive methods require endoscopy and include biopsies of gastric tissues for the histology, culture, and rapid urease test (RUT) and non-invasive tests include serologic tests, urea breath test and fecal antigen tests. By increasing the use of antimicrobials, approximately 20% bacterial resistance to antibiotics has been reported, particularly where antimicrobials are readily available without a prescription. Indications to treat and eradicate *H. pylori* infections include gastric and duodenal ulcers, a positive familial history of gastric cancer, MALT lymphoma and primary gastric cancer (15). Various therapeutic regimes with different effectiveness and side effects have been suggested to eradicate *H. pylori* infection. The reason for the diversity of these diets can be attributed to the difficulty of treating *H. pylori* and sometimes developing resistance to certain kinds of medications (16). Diet therapy, which has been approved and used as a first-line treatment by many countries, including Iran, is a three-drug regimen including a proton pump inhibitor (PPI) and clarithromycin with either amoxicillin or metronidazole administered for 14 days; this diet is also known as standard triple therapy (STT) (17,18). Over the past few years, the effectiveness of standard triple therapy has gradually declined (less than 80%) (19-21). This decline is particularly marked in the Mediterranean area (22). Due to the progressive decline in the utility of traditional diets, novel approaches to the treatment of *Helicobacter pylori* have been proposed. One promising approach is sequential treatment. This diet consists of two induction phases, a proton pump inhibitor (PPI)/ amoxicillin, and a second phase consisting of PPI and two antibiotics (furazolidone and clarithromycin) (23).Clinical experiences in Iran and in the most developing countries have shown that the rate of eradication of *H. pylori* using the same treatment regimens is much lower than that in Western countries and also the rate of recurrence or re-infection in the short or long term is much higher than what has been reported in Western countries (24).This has led to an expansion of research on alternative treatment regimens of primary intent. The objective of this study was to assess the eradication of *Helicobacter pylori* using levofloxacin-containing regimens and compare it to clarithromycin-based regimens.

Material and Method

This study was designed as a clinical trial (IRCT20170803035490N1) study.

A total of 170 patients with *Helicobacter pylori* referring to Besat gastrointestinal clinic in Kerman in 2019 were included in the study Block-balanced randomization was used to allocate patients to either group A or group B with a block size of 2. A statistician developed block-balanced sequences based on computer-generated random numbers. Patients were divided into two groups of 85. Participants were aware of the type of treatment and the study was not blind. Patients between the ages of 18 and 65 years presenting with upper gastrointestinal symptoms underwent upper endoscopy. If there was the evidence of inflammation, swelling or

ulcers and erosion, biopsy was taken from the antrum and submitted to a pathology lab, or a rapid urease test (RUT) was performed (if not receiving any bismuth or antibiotics in the last 4 weeks and be off PPI therapy for 2 week prior to the performing endoscopy). Since the sensitivity of the biopsy urease test is approximately 90 to 95% and its specificity is 95 -100%, false positives are unusual. However, recent gastrointestinal bleeding or the use of PPIs, H2 blockers, antibiotics, and bismuth-containing compounds may lead to false negative test. To perform rapid urease test, Man company kit under the license of Elitech group was used. Based on the results of tests and endoscopic findings such as peptic ulcer or erosion, patients were assigned as candidates for eradication of *Helicobacter pylori*. To prevent selection bias, patients were allocated into two groups of treatment regimens using block randomization method. Patients were informed about the type of treatment and informed consent was obtained. Group A included 85 patients treated with the standard clarithromycin (fromilid) 500 mg twice daily and pantoprazole (nolpaza) 40 mg twice daily and amoxicillin 1.0 g twice daily for 14 days. Group B (85 patients) received 250 mg pantoprazole, amoxicillin and levofloxacin (Tavanic®) twice daily. If allergic to amoxicillin, the patient would receive 500 mg of metronidazole twice daily and be excluded from the study. One month following completion of the treatments, the patients were referred to the laboratory for stool antigen tests. Experiments were performed in a laboratory with the necessary quality control standards: Stool antigen test was used for detection of *Helicobacter pylori* after eradication therapy which has a sensitivity of 94% and a specificity of 88% to 92%. The Fecal H pylori Ag ELISA Kit (Epitope Diagnostics, Inc.) was used for this purpose. The criterion for a microbial response was a negative stool antigen test one month after the completion of treatment. Exclusion criteria included gastrointestinal bleeding, allergic reaction to antibiotics, intolerance to drug side effects and lack of evidence for clinical response to standard clarithromycin treatment.

Ethical considerations

All participants provided informed written consent to be part of the study after a detailed description of the study treatment. This study was approved by the Ethics Committee of Kerman University of Medical Sciences in Iran (Ethical Code: IR.KMU.AH.REC.1395.42)

Results

This study was performed as a clinical trial on 170 patients. We calculated that 85 participants were required to be enrolled in each study group in order to achieve 80 % power and finally enrolled a total of 100 patients in each group to allow for probable loss in follow-up or cases that might not be evaluable for the primary outcome. During the study, 200 patients with epigastric symptoms referred to Besat Gastroenterology Clinic in Kerman who underwent upper endoscopyand showed *Helicobacter pylori* infection based on pathological results. These individuals were divided into two groups of A and B using randomized block design. Group A received standard treatment containing clarithromycin and group B received levofloxacin-containing diet (Figure1).

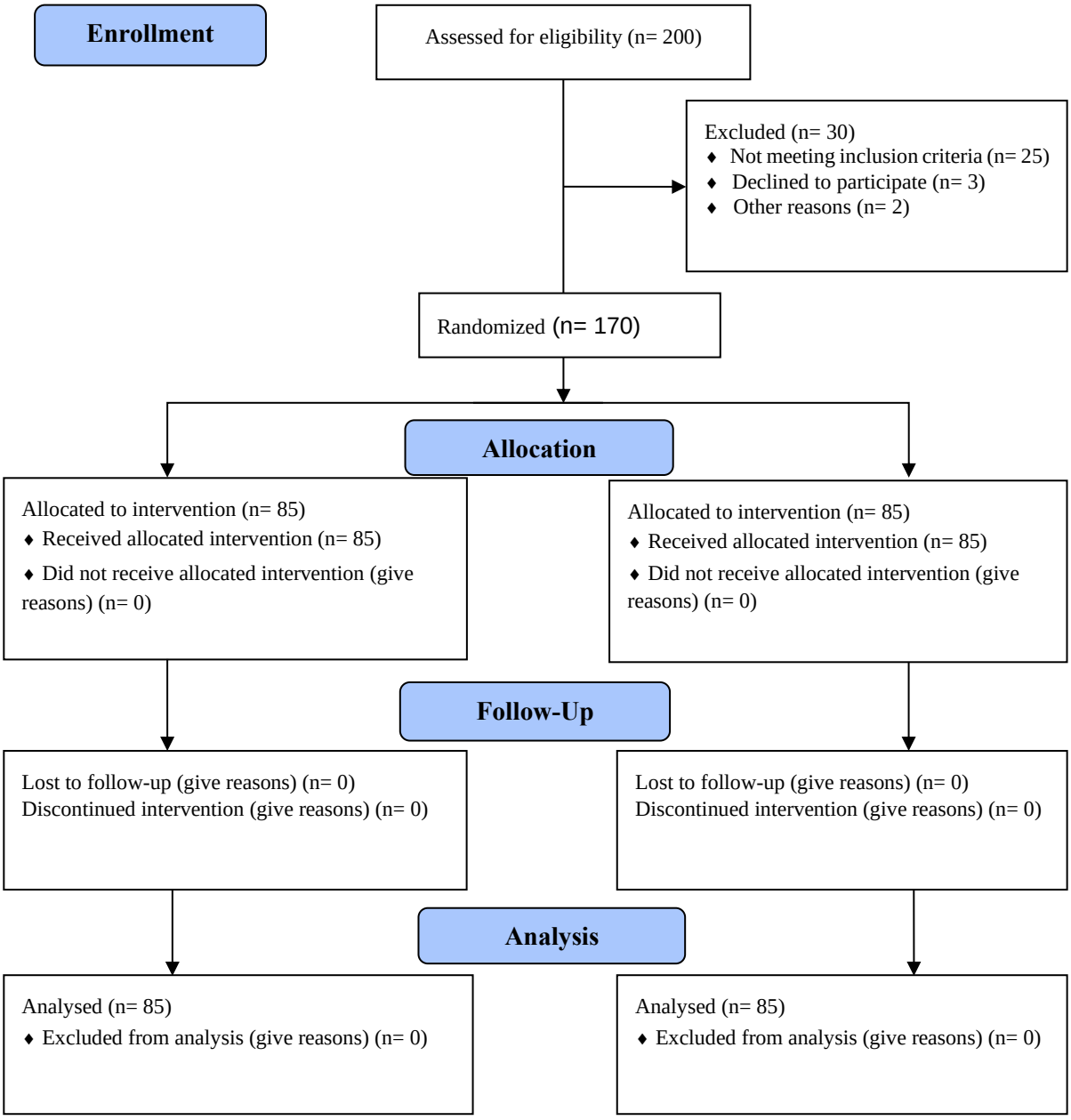


Figure 1. Consort flow diagram for two groups of patients

The mean age of patients in groups A and B was 42 ± 11.88 and 41 ± 13.75 years respectively and 62 patients were in the age group of 31-40 years. There was no statistically significant difference between the two treatment groups in terms of patients' age. In term of sex, 81 patients were men and 89 were women. There was no significant difference between the treatment groups A and B in terms of sex according to the statistical analysis. In group A 49.4% and in group B 45.8% were male respectively (P=0.805).

Other demographic characteristics of patients participating in this study, including: education, smoking (cigarette and hookah) were also investigated. Out of 170 patients studied in this study, in different groups of education, the highest frequency was related to people with high school diploma (69 people, 49.9% and 35.3% in groups A and B respectively).The

results on the frequency of smoking was 65 people. In group A, 35 people and in group B, 30 people were smoker. There was no significant difference between the groups in terms of level of education and smoking (p= 0.309 and p=0.763 respectively, Table 1, Graphs 1-4).

Table 1. Demographic information of patients in the two studied groups

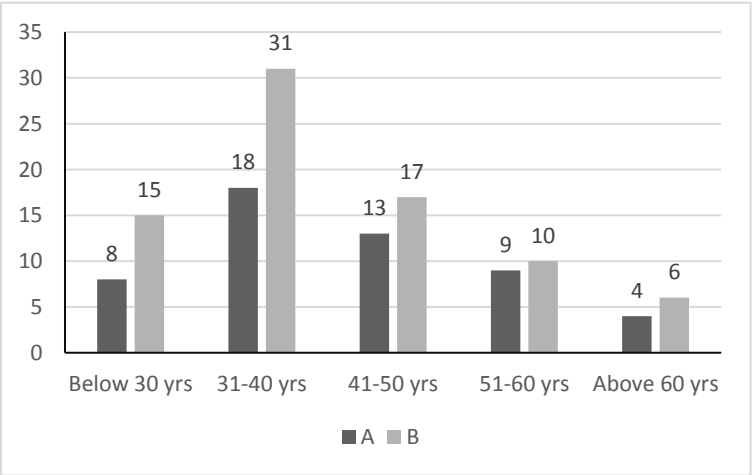
		A		B		
		n	**%**	**n**	**%**	**p.v**
Age	**Below 30 yrs**	15	17.6	16	18.8	0.545
	31-40 yrs	28	32.9	34	40	
	41-50 yrs	21	24.7	18	21.1	
	51-60 yrs	14	16.4	11	12.9	
	Above 60 yrs	7	8.4	6	7.2	
Gender	**Male**	42	49.4	39	45.8	0.805
	female	43	50.6	46	54.2	
Education	**Illiterate**	13	15.3	9	10.6	0.309
	Under diploma	11	12.9	18	21.2	
	diploma	39	45.9	30	35.3	
	University	22	25.9	28	32.9	
Tobacco	**no**	50	58.8	55	64.7	0.763
	Cigarettes	11	12.9	9	10.6	
	hooka	14	16.5	12	14.1	
	Cigarettes, hooka	10	11.8	9	10.6	

As shown in table 2 the success rate for H. pylori eradication in the two group showed a significant difference and it was higher in group B than in group A.

Table 2. Frequency of *Helicobacter pylori* eradication in the two studied groups

Group	A		B		p-value
Eradication of *Helicobacter pylori*	N	%	N	%	
Eradicated	52	61.1	79	92.9	0.037
Not eradicated	33	38.9	6	7.1	

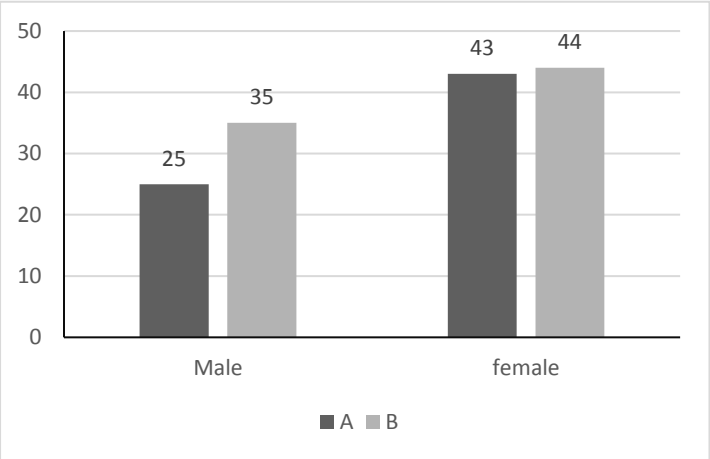
In comparing the eradication rate between different age groups, there was no statistically significant difference between the age groups (p=0.825). The frequency of Helicobacter pylori eradication based on age is shown in graph 1.



Gragh 1. The frequency of Helicobacter pylori eradication based on age

The mean age of patients in groups A and B was 42 ± 11.88 and 41 ± 13.75 respectively. 62 patients were in the age group of 31-40 years. There was no significant difference between the treatment groups in terms of patients' age according to statistical analysis (P= 0.545).

There was no significant difference in the eradication rate of *Helicobacter pylori* based on gender in any of the treatment groups. In both groups the higher eradication rate was in women than men (62.7% vs. 59.5% in group A and 95.6% vs. 89.7% in group B. The frequency of Helicobacter pylori eradication based on gender is shown in graph 2.

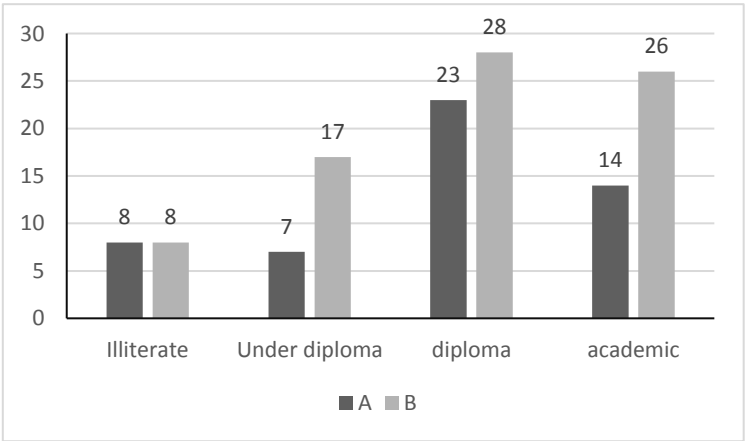


Gragh 2. The frequency of Helicobacter pylori eradication based on gender

There was no significant difference between treatment groups A and B in terms of gender according to statistical analysis. In group A 49.4% and in group B 45.8% were male respectively (P= 0.805).

In none of the two groups, *Helicobacter pylori* eradication rate based on education level was significant. The highest frequency of eradication in both groups is for diploma cases. The frequency of Helicobacter pylori eradication based on education is shown in graph 3.

No association between *H. pylori* prevalence and smoking in both groups was found (Table 3).



Gragh 3. The frequency of Helicobacter pylori eradication based on education Out of 170 patients studied in this study, in different groups of education, the highest frequency was related to people with high school diploma with 69 people, 49.9% and 35.3% in groups A and B respectively (P= 0.309).

Table 3. The frequency of Helicobacter pylori eradication based on tobacco use in the two studied group

Group	B			p.v	A			p.v
Tobacco	%	Eradicated	Total		%	Eradicated	Total	
Do not consume	96.3	53	55		60	30	50	**0.902**
Cigarettes	88.8	8	9		63.6	7	11	
hookah	83.3	10	12	0.838	64.2	9	14	
hookah and Cigarettes	88.8	8	9		60	6	10	

In this study, 10 out of 170 patients reported side effects. Side effects (nausea, vomiting, and diarrhea) were reported by 6 people in group A and 4 people in group B. However, no statistically significant difference was found between the groups in terms of the incidence of side effects (P= 0.772)

Among the side effects, the highest frequency was related to abdominal pain in 4 patients, nausea in 3 patients, vomiting in 2 patients and diarrhea in 1 patient. The frequency of eradication did not differ significantly between the two groups in terms of drug side effects. The *H. pylori* eradication rates in patients with and without side effects to the drugs proposed in the study were respectively 50% and 62% in group A and 100% and 92.5% in group B.

Discussion

In this study, eradication of *Helicobacter pylori* with a 14-day levofloxacin-containing triple regimen consisted of levofloxacin, amoxicillin, and pantoprazole was more effective. In a study in Hong Kong (2009), Hung has compared the diets of clarithromycin and levofloxacin. The first group was given levofloxacin 500 mg daily, amoxicillin 1 g twice daily and omeprazole 20 mg twice daily for one week. In the second group, 500 mg clarithromycin was administered twice daily instead of levofloxacin. The eradication rate was 85.3% with levofloxacin diet and 92.7% with clarithromycin diet (p = 0.43) and complications were more common in clarithromycin treated group (21.3% vs. 13.3%, p = 0.06) (25). In Richard *et al* study at the University of Michigan, the eradication rate of *Helicobacter pylori* with levofloxacin triple therapy was higher than that of the bismuth-based quadruple therapy (68% vs. 87%) and it was better tolerated by patients (26). Gopal *et al*. (2013) compared the standard triple diet (containing clarithromycin) and levofloxacin-based diet for eradication of *Helicobacter pylori*. The eradication rate was almost the same (69% vs. 80%) and they proposed levofloxacin- based regimen as a more economical option (27). In a study conducted by Goudarzi *et al*. on the resistance of *Helicobacter pylori* to common antibiotics, they found that the lowest resistance (13.4%) was related to levofloxacin and resistance to clarithromycin was 43.1% (28).Haji-Aghamohammadi *et al* compared the efficacy of levofloxacin versus clarithromycin in the eradication of *Helicobacter pylori* infection and concluded that despite the same safety, levofloxacin-based regimen had better efficacy (29). In a study by Khademi *et al.* in a multicenter analysis of *Helicobacter pylori* resistance from 1997 to 2013 in Iran, levofloxacin with 5.3% resistance and metronidazole with 61.6% resistance had respectively the lowest and highest antibiotic resistance rates (30). Clinical experience in Iran and in most developing countries has shown that the rate of eradication of *Helicobacter pylori* using the same treatment regimens was much lower than the rate reported in Western countries and the rate of recurrence or re-infection in the short or long term was much higher than the rate reported in Western countries (31). In recent years, there has been a significant reduction in the success rate of *Helicobacter pylori* eradication using standard drug regimens worldwide, especially in Asian countries (32). Researchers have stated that one of the main reasons for this is the increase in resistance of *Helicobacter pylori* to various antibiotics, particularly clarithromycin and metronidazole (33). In the present study, we examined patients for side effects during the course of drug treatment and also after the end of the treatment period, and the obtained data were collected based on the patients' own statements. Side effects studied included nausea, vomiting, abdominal pain, and diarrhea. In this study, out of 179 patients, 10 reported side effects. In a study by Kongchayanun *et al*. in China (2011), the most important side effects were nausea, vomiting, dizziness, and bad taste in the mouth (34). In a study conducted by Moradniani *et al*. in 2018 on Levofloxacin- based versus

clarithromycin- based sequential therapy in *helicobacter pylori* eradication, they found that the sequential levofloxacin-based treatment was more effective in eradicating HP than sequential clarithromycin-based treatment (35). In our recent study, it was found that levofloxacin-based therapy can be more effective than standard clarithromycin-based therapy.

In a study conducted by Fakheri *et al*, due to the high eradication rate of Helicobacter pylori and the very low rate of severe side effects, triple treatment with levofloxacin seems to be a suitable second-line option in the case of previous failure by treatments containing clarithromycin (36). This finding is similar to our results in the present study.

In another study conducted by Tirgar Fakheri *et al*. both triple therapies containing clarithromycin and levofloxacin do not appear to be suitable options for eradicating first-line Helicobacter pylori in Iran, and they recommended the use of clarithromycin in quadruple diets and storage levofloxacin for use in the second-line eradication regimens (37).

In the study done by Tariq *et al*., there was a significantly lower eradication rate with triple levofloxacin treatment among selected US population. Therefore, this treatment was not found as a good first-line treatment in US population, and a clarithromycin-based diet was suggested (38). Their conclusion is the opposite of our results.

In reviewing similar studies, in terms of the prevalence of side effects, we found that the complications and their incidence varied remarkably in different studies that were not consistent with our study. The problem may be due to racial differences; however, in all of the aforementioned studies, there was no significant relationship between the incidence of side effects and the eradication rate of *Helicobacter pylori*.

The acceptable rate of eradication of *Helicobacter pylori* in a standard diet should be 85-90% or higher, which is an acceptable limit. So far, very few studies have been conducted comparing fairly similar treatment regimens with this study, and no similar studies have been conducted in Iran. Most studies have investigated other diets or had longer treatment periods.

Conclusion

According to the results of the present study, it can be concluded that the eradication of *Helicobacter pylori* in the 14-day treatment regimen of levofloxacin, amoxicillin and pantoprazole is more effective than the standard regimen of clarithromycin, amoxicillin and pantoprazole. Since the acceptable rate of eradication of *Helicobacter pylori* in a standard diet is expected to reach a minimum of 85-90% cure, the rate of eradication of *Helicobacter pylori* in group B of the present study was standard and in group A was less than standard which requires further research in this area.

Limitation

Limitations of this study included the presence of underlying disease, lack of education and blindness and psychological disorders, drug interactions, lack of proper cooperation in the timely use of drugs and withdrawal from the study at any stage of the study. To overcome these limitations, patients with no underlying problems were tried and for illiterate and blind patients, specific plastic boxes were used in which the medications were taken each time. Also, the daily medications of the patient were examined by the researcher and interfering drugs were removed. All participants asked for studying and signing the informed consent form and all the clauses of this form were explained for them by the researcher.

Acknowledgments

This study was reviewed by the Ethics Committee at Kerman University of Medical Sciences and approved with the code IR.KMU.AH.REC.1395.42. We, hereby, appreciate the efforts of all the staff of the Endoscopy Unit of Besat Gastroenterology Clinic who have helped us in this research.

Conflict of interest

Authors declare that there is no conflict of interest.

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