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Comparing Regimens Based on Clarithromycin, Furazolidone, and Levofloxacin in Patients With Helicobacter Pylori Infection: A Clinical Trial

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Abstract

Background: There is no current and broad consensus about the eradication of Helicobacter pylori (HP) infection in gastric ulcer and indigestion diseases.

Objective: This study aimed to compare three regimens based on clarithromycin, furazolidone, and levofloxacin in patients with HP infection.

Materials and Methods: This study was a randomized clinical trial examining 102 patients with gastrointestinal diseases. They were randomly assigned to three equal groups. In the first group, basic medication (i.e., a combination of esomeprazole 40 mg and amoxicillin 1000 mg) with clarithromycin 1000 mg was prescribed. The second group was treated with basic medication regimen along with furazolidone 400 mg. And the third group was given the basic medication with levofloxacin 500 mg. Eradication rates of the HP infection and incidence rates of drug side-effects in the three groups were compared after two-week and the obtained data were analyzed using appropriate statistical methods.

Results: According to our study results, the HP infection eradication rates revealed by the per-protocol (PP) and intention-to-treat (ITT) analyses for the levofloxacin group were 91.2% and 93.8%, respectively, which were significantly different from those found for the furazolidone group by PP analysis and for the clarithromycin group by PP and ITT analyses ($P<0.05$). Moreover, there were no significant differences among the three groups regarding the side effects ($P>0.05$).

Conclusion: It was concluded that two-week regimen of levofloxacin together with a single-dose of esomeprazole and amoxicillin was desirable (90%-95%) and more effective than furazolidone and clarithromycin in eradicating HP.

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Background

Helicobacter pylori (HP) is the most common cause of chronic bacterial infection and has been identified as the main cause of peptic ulcer and chronic active gastritis[1,2]; it exists in an accumulated form in the stomach of more than 50% of the world's population. According to results from worldwide studies, the prevalence of HP is currently 30% to 50% in developed countries, and it is more than 50% in developing countries.[3,4] As for Iran, the figure for the prevalence is estimated to be between 50% to 60%.[5] The prevalence of HP infection in adults is far more than that in children, and it afflicts men more than women.[6-8] Therefore, it is of a particular importance to include demographic characteristics in a research exploring this bacterium.

After almost 30 years since the discovery of HP, no specific regimen has been proposed for the eradication of this infection in patients so far. To deal with this problem, different treatment regimens with diverse effects on the pathogens have been recommended.[9]

Selecting a suitable HP treatment regimen depends on the type and price of the drugs, availability, side effects, consumed facilities, patient conditions and drug resistance; moreover, whether the considered method is aggressive or not is of great importance.[10] Several studies have introduced proton pump inhibitor (PPI) as the main element of a three-drug regimen for HP eradication[11,12]; however, recent studies have considered other methods as being more effective.[13,14] Despite all the new treatments, there is still 10%–25% treatment failure in the given cases.[15,16] Addressing this problem requires further researches on the development of treatment regimens against HP.

In different regions, various medication regimens are

used against this bacterium. As for Iran, many treatment regimens have been administered by researchers,[17] which mostly emphasize regimens based on clarithromycin or furazolidone.[18-20] In addition, levofloxacin has been found effective in HP eradication in various studies. In a study by Kuo et al,[21] for example, levofloxacin-based regimen was discovered to be more effective than the regimen without it in eradicating HP infection. Since there is no general consensus on the HP infection eradication, this study aimed to compare three triple regimens based on clarithromycin, furazolidone and levofloxacin in the patients with HP infection in Qazvin city, Iran.

In the present study, furthermore, single-dose esomeprazole 40 mg was administered and two-weeks treatment period was considered for HP infection treatment.

Materials and Methods

The present study was a randomized clinical trial performed in Gastroenterology Clinic of Velayat hospital in 2018, Qazvin, Iran. Participants of this study included 102 patients who had positive pathological and laboratory test results for HP infection and suffered from persistent gastrointestinal symptoms. The study was conducted in accordance with the research priority of Qazvin University of Medical Sciences and was approved by the university's Ethics Committee. The inclusion criterion was undergoing endoscopy with positive rapid urease test (RUT), and the exclusion criteria were smoking, Used nonsteroidal anti-inflammatory drugs (NSAIDs), having gastrointestinal bleeding and gastric cancer, using a compound of proton pump inhibitor (PPI) during the last two weeks, and consuming antibiotic during the previous month.

Patients were randomly assigned to three groups, each including 34 people. To this end, every patient was given a number from a sealed envelope. The numbers were then randomly selected by a computerized table containing randomized numbers. As for the first group, basic medication (i.e., a combination of esomeprazole 40 mg and amoxicillin 1000 mg) with clarithromycin 1000 mg every 12 hours was prescribed. The second group was treated with basic medication regimen together with and furazolidone 400 mg every 12 hours. And the third group received the basic medication with levofloxacin 500 mg every 12 hours. The three regimens were administered for two-weeks.

All patients received serious warnings about smoking and taking painkillers such as aspirin and similar medications during the course of treatment.

At the end of every week, the patients were asked to report any complaints including headache, emerging nausea, emerging abdominal pain, and symptoms of allergy increase such as itching, hives or tendinitis. Fourteen days after the completion of the stool antigen test, the organism was sent to the laboratory in order for investigating the eradication and, finally, the HP infection eradication rate and incidence rate of drug side effects were determined and compared in the three groups. Negative stool antigen test and the lack of gastrointestinal complaints were considered as the indicators of HP eradication.

Patient-related data including age, gender, clinical symptoms, and drug side effects along with HP stool antigen results were recorded in appropriate forms. All patients' data were entered into SPSS (ver. 22). Not receiving the full medication dosage was considered as a failure to compliance; therefore, two intention-to-treat (ITT) and pre-protocol (PP) analytical methods were performed for the patients. According to the anthropometric data such as age and height, chi-square test was used for the preliminary comparison of different treatment groups. The Cochran-Mantel-Haenszel method was applied for comparing eradication rate in all three groups (ITT-based and PP-based). The $P < 0.05$ was considered as the level of significance.

Results

A total of 102 patients including 62 (60.8%) women and 40 (39.2%) men participated in this study. These patients were randomly divided into three 34-people groups and underwent the treatment. Endoscopic examinations initially showed that erythema antrum was the most prevalent finding in all three groups, and normal endoscopy and duodenal ulcer ranked next in this regard (Figure 1).

Out of 102 participants, 94 ones completed the study according to the protocol but 8 patients including two from the levofloxacin group, three from the furazolidone group, and three from the clarithromycin group failed to complete it due to personal reasons. Since the patients did not receive their full medication dosage, it was considered as the failure to compliance.

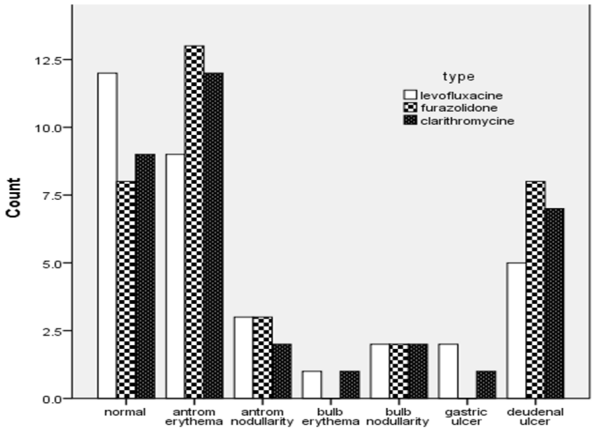

Figure 1. Endoscopic Examination in Three Groups.

The treatment groups (ITT-based and PP-based) were compared based on the demographic characteristics in the baseline. Adopting both treatment protocols, no significant differences were observed among the three groups in terms of age and gender ($P > 0.05$, Table 1).

Table 2 shows eradication rates per treatment protocol of the three treatment groups. In both protocols, clarithromycin had the minimum eradication rates, whereas levofloxacin had the maximum eradication rates (Table 2). As for the PP-based population, eradication rate of levofloxacin was 1.70 times higher than that of clarithromycin (95% CI: 1.20 to 2.37), and the Mantel-Haenszel test was 12.23 with $P < 0.001$. As for the ITT-based population, the eradication rate of levofloxacin was 1.73 times higher than the value obtained for clarithromycin (95% CI: 1.23 to 2.40), and the Mantel-Haenszel test was 10.01 with $P=0.002$. As far as the PP-based population was concerned, the eradication rate of levofloxacin was 1.26 times higher than the value obtained for furazolidone (95% CI: 1.008 to 1.58), and the Mantel-Haenszel test was 4.49 with $P=0.034$. As for the ITT-based population, no significant relationship was found between levofloxacin and furazolidone ($P=0.07$). As for the PP- and ITT-based population, in addition, no significant relationship was detected between furazolidone and clarithromycin ($P > .05$).

Regarding the incidence of side effects during the treatment, two patients suffered from nausea and one had tendinitis in the levofloxacin group, as well as two patients had nausea in the furazolidone group and two had nausea in the clarithromycin group. However, these patients completed the research and the side effects did not stop them following the treatment.

Table 1. Comparing Demographic Characteristics in Three Treatment Groups

Parameter	Treatment Groups			*P* Value
	Clarithromycin	Furazolidone	Levofloxacin	
PP Population				
Age				0.07
<40	6 (19.4%)	14 (45.2%)	11 (34.4%)	
40-60	24 (77.4%)	15 (48.4%)	16 (50%)	
>60	1 (3.2%)	2 (6.5%)	5 (15.6%)	
Gender				0.86
Female	18 (58.1%)	20 (64.5%)	20 (62.5%)	
Male	13 (41.9%)	11 (35.5%)	12 (37.5%)	
ITT Population				
Age				0.08
<40	8 (23.5%)	16 (47.1%)	12 (35.3%)	
40-60	25 (73.5%)	16 (47.1%)	17 (50%)	
>60	1 (2.9%)	2 (5.9%)	5 (14.7%)	
Gender				0.96
Female	20 (58.8%)	21 (61.8%)	21 (61.8%)	
Male	14 (41.2%)	13 (38.2%)	13 (38.2%)	

able 2. Level of Eradication in Each of the Three Groups Under Treatment

Treatment groups	Eradication	
	Number	Percent
PP		
Levofloxacin	30	93.80
Furazolidone	23	74.20
Clarithromycin	17	54.80
ITT		
Levofloxacin	31	91.20
Furazolidone	24	70.60
Clarithromycin	18	52.90

Discussion

There is no current and general consensus about the eradication of HP infection in gastric ulcer and indigestion diseases (22), which necessitates further researches to resolve the given non-consensus. In this study, the efficacy of three treatment methods for HP eradication were compared. According to the results from the comparison, the levofloxacin group had the highest eradication rate and furazolidone and clarithromycin groups had the second and third ranks, respectively.

Eradication rate was statistically considerable between the levofloxacin and clarithromycin groups in both treatment protocols so that for the PP- and ITT-based groups, the eradication probabilities of levofloxacin and clarithromycin were 1.70 and 1.73 times higher, respectively. These differences indicated that the levofloxacin-based triple treatment was more effective than clarithromycin-based triple treatment in eradicating HP infection. Haji-Aghamohammadi et al demonstrated that levofloxacin-based triple treatment produced more positive effects than clarithromycin-based triple treatment.[23] Furthermore, Gopal et al found that the HP eradication rates in the clarithromycin-based regimen – compared to levofloxacin-based regimen, were 69% and 79% in ITT analysis, respectively; whereas they were 80% and 87% in PP analysis, respectively.[24] Moradniani et al reported similar results in their study and showed that the eradication rates in the levofloxacin group for PP and ITT analyses were 87.6% and 85.1%, respectively.[25] They also demonstrated that consecutive levofloxacin-based treatment was more effective than consecutive clarithromycin-based treatment in eradicating HP.[25] Efficacy of consecutive levofloxacin-based treatment might have been due to the low resistance to levofloxacin or high resistance to clarithromycin.[26] Their finding was confirmed in a study by Romano et al.[27] Most studies conducted in different countries have shown low

resistance to levofloxacin in the HP strain.[28,29] Similarly, a low resistance to levofloxacin has been reported by studies carried out in Iran.[28]

Furazolidone is an effective alternative for the combined treatment for HP eradication. This antibiotic, compared to amoxicillin or metronidazole, leads to an appropriate eradication in the patients with treatment failure. However, it has not been widely used due to its reported side effects,[30,31] which was the reason behind its exclusion from our study and the comparison of drug regimens. Nevertheless, its eradication rate was lower than that of levofloxacin but higher than that of clarithromycin. This eradication rate was below the average rate (80%) and was not considerably higher than that of clarithromycin. A closer investigation revealed that in the furazolidone group, levofloxacin was considerably superior to furazolidone only in the PP-based protocol; the eradication probability of levofloxacin was 1.26 times higher than that of furazolidone, whereas no significant relationship was observed between furazolidone and levofloxacin in the ITT-based treatment group. Contrary to our finding, Eisig et al found that the eradication rate of this bacterium for the Brazilian population was 89% and 88% for PP and ITT analyses, respectively, which was more than the average rate (80%).[32] It should be noted that there may have been furazolidone-resistant strains in some areas. Therefore, it was recommended that further researches be conducted in different regions with more sample sizes to prove this hypothesis.

The results of our study showed that the eradication rate with clarithromycin regimen was between 50% to 60%, which was lower than the average rate of 80%; this result might have been different from other study findings.[27,33] Such a difference could have been attributed to different basic medication types used along with clarithromycin. One reason might have been the resistance to clarithromycin; and one of the causes for this resistance to clarithromycin in different communities was attributable to the use of macrolides usually prescribed for treating respiratory diseases.[34] This resistance is higher at younger ages, which requires sufficient academic attention in different communities in order for developing appropriate preventive measures against the disease.

As for the incidence of side effects, two patients had nausea and one patient had tendinitis in the levofloxacin group, two patients had nausea in the furazolidone group, and two participants had nausea in the clarithromycin group. In statistical terms, there was no significant difference between drug side effects and adjustment in both regimens. Similarly, Romana et al found that the most common side effects developed after levofloxacin and clarithromycin administration were abdominal pain, diarrhea, severe tendon, and nausea.[27]

Since the prevalence of HP infection is much higher in adults compared to children and the infection afflicts men much more than women,[7] this study examined the differences in age and gender in two treatment protocols. However, no significant differences were found in the results for three treatment groups in either of the two protocols, which was in complete agreement with the finding from a study by Zamani et al.[7]

The present study faced some the limitations, one of which was its single centrality and low sample size. Therefore, prospective studies with larger sample sizes were required before generalizing the obtained results.

Conclusion

According to our study results, levofloxacin was more effective than furazolidone and clarithromycin in eradicating HP, and its effectiveness was above the average rate (80%). Moreover, our more detailed investigation showed that levofloxacin was considerably preferred to clarithromycin and furazolidone. Our study was also characterized by fewer consumed drugs per day and shorter medication treatment duration.

No significant difference was found between the two groups regarding the incidence of side effects. Considering higher eradication rate in other studies for clarithromycin, it seemed that the resistance to this antibiotic was increasing in the given region, which needed to be confirmed via conducting more detailed studies.

Authors' Contributions

NG did the design, data gathering, and manuscript preparation. AS did the data gathering, analysis, and manuscript preparation. AH did the design, data gathering, and manuscript preparation. All authors read and approved the final manuscript.

Ethical Approval

This study was approved by the Ethics Committee of Qazvin University of Medical Sciences and the participation of individuals was subject to a written consent (Ethics committee reference number: IR.QUMS.REC.1396.62). Moreover, this study was registered by Iranian Registry of Clinical Trials (identifier: IRCT2016040318124N4; https://www.irct.ir/trial/16533)

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

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