# Comparison of Standard Triple Therapy Regimen with Sequential Therapy Regimen Containing Levofloxacin Used for The Eradication of Helicobacter Pylori in Patients with Gastrointestinal Infection Caused by Helicobacter Pylori

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## Abstract

Objectives: The aim of this study was to compare standard triple therapy regimen with sequential therapy regimen containing levofloxacin used for the eradication of H. pylori in patients with gastrointestinal infection caused by H. pylori.

Methods: This single blind clinical trial study was conducted on 96 patients with positive Rapid Urease Test (RUT) who were referred to the Endoscopy center of Hajar Hospital in Shahrekord city, located in southwest of Iran. The patients were randomly assigned into two treatment groups: sequential therapy regimen and triple therapy regimen. The patients in the first group received sequential therapy regimen including omeprazole, amoxicillin, levofloxacin, and tinidazole; the second group of patients received a triple therapy regimen consisting of omeprazole, amoxicillin, and clarithromycin. Four weeks after the end of the treatment, using H. pylori Stool Antigen (HpSA), a test was performed to prove the eradication of H. pylori. The influences of patients' age, gender and eradication level were also investigated.

Results: There were significant differences between the two groups in terms of age and education. While H. pylori eradication rate was 67.3% in the sequential therapy regimen, it was 66% in standard triple therapy regimen. In addition, among patients receiving triple therapy regimen, being aged older than 40 years had a significant relationship with eradication. Moreover, in patients receiving sequential therapy regimen, education level had a significant relationship with eradication.

Conclusion: There was no statistically significant difference between the two therapy groups in terms of H. pylori eradication rate. However, given the low rates of H. pylori eradication in both sequential and triple therapy regimens observed in the present study, it seems that it is necessary to conduct further research on the bacterial resistance to the prescribed antibiotics.

Key words: H. pylori, standard triple therapy, sequential therapy, Eradication

## Introduction

H. pylori is a microaerophilic gram-negative bacterium which has affected more than half of the world population [1-6]. Infections caused by H. pylori are known as the main cause of chronic gastritis disease type B, peptic ulcer, and mucosa associated lymphoid tissue (MALT) lymphoma; in addition, the treatment of related infections are recommended to prevent adenocarcinoma gastric cancers [7-14]. The guidelines proposed for the treatment of H. pylori infection have emphasized on the eradication of the bacteria using multiple medication regimens [15]. Nevertheless, treatment success rate depends on several factors including type of antibiotic, dosage, formulation, duration of treatment, patient compliance, smoking, and bacterial resistance to one or more antibiotics [16]. Resistance to antibiotics is the most common cause of failure in achieving an eradication rate of higher than 80% [12, 17, and 18]. Moreover, using the same regimens, the rates of relapse and re-infection in developing countries are higher than those in other countries [19].

According to studies conducted in Iran, the prevalence of H. pylori resistance to clarithromycin, furazolidone, and metronidazole is remarkably increasing and the level of resistance to amoxicillin is much higher than that in other countries [20, 21]. Hence, as the result of the increase in bacterial resistance to common antibiotic regimes and differences in resistance patterns in different regions, there have been some differences in therapy regimens and techniques used in different areas [22-24]. Quadruple therapy is a conventional therapy regimen which consists of a proton pump inhibitor drug, amoxicillin, metronidazole, and clarithromycin [15,25-27]. Resistance to clarithromycin and metronidazole has increased in recent years. Resistance to metronidazole has also been observed in 40-50% of people in developed countries and 80% of people in developing countries [12]. In Iran, the prevalence of resistance to clarithromycin and metronidazole are about 16.7% and 57.5%, respectively [21].

Sequential therapy is one of the methods which have had promising outcomes in recent years. Using sequential therapy, an eradication rate of more than 80% has been achieved and patients have tolerated it well [12]. Vaira and colleagues compared two regimens of triple therapy and sequential therapy for 10 days; According to their findings, using triple therapy and sequential therapy regimens, eradication rates of 77% and 89%, respectively, were achieved. It shows that sequential therapy had resulted in higher eradication rate, in comparison with the standard triple therapy [28]. In Polat 's study, H. pylori eradication rate was significantly higher in the group undergoing sequential therapy, compared to the group undergoing triple therapy [29].

To avoid treatment failure and the development of secondary resistance to antibiotics, it is necessary to select an appropriate treatment regimen as the first line treatment; hence, it is of great value to conduct research to evaluate the effectiveness of common therapy regimens for the eradication of the bacteria, compare these methods and finally identify the most effective and the safest treatment regimen. Moreover, Levofloxacin is a medication that is commonly used in such therapy regimens and it has been introduced into the pharmacopoeia of Iran in recent years. Therefore, to identify an effective treatment regimen to reduce antibiotic resistance and to achieve bacteria eradication, this study aimed to compare standard triple therapy regimen with sequential therapy regimen containing levofloxacin used for the eradication of H. pylori in patients with gastrointestinal infection caused by H. pylori.

## Materials and Methods

**Study population**

This single blind clinical trial was conducted on 96 patients with dyspepsia and positive Rapid Urease Test (RUT) who were referred to the endoscopy center of Hajar Hospital in Shahrekord city, located in southwest of Iran, from May to August 2015. This study was approved by the Ethics Committee of Shahrekord University of Medical Sciences, Shahrekord, Iran. Eligible patients were selected in the study period. Patients with drug resistance and drug intolerance or other complications and those unwilling to continue the study were excluded. To determine the sample size, we considered the quantitative changing condition of the sample size and took into account the Type I error (α) of 0.05 and Type II error (β) of 0.20 (power of 80%); accordingly, the sample size was determined as 50 patients per group.

The patients with dyspepsia and positive RUT who were referred for outpatient services and admitted to endoscopy center were randomly assigned to one of the two groups. To maximize the randomization process and assign patients to the groups, the necessary medications for each group were taken out of their packages and were placed in opaque envelopes whose content was not visible. The envelopes were titled by the letters A and B; each letter represented a particular treatment group. Patients were not aware of the type of treatment group. Each patient received a piece of paper on which type of therapy regimen was determined by the letters A (triple therapy regimen) or B (sequential therapy regimen containing levofloxacin). All the patients were trained about how to take the drugs; then, the patients were asked to visit their physician whenever they experienced any problems during treatment, especially when facing drug complications or being forced to discontinue the treatment.

After assigning the patients to the groups, the patients in Group A who were under triple therapy for 10 days, received omeprazole 20 mg twice a day, amoxicillin 1 g twice a day, and clarithromycin 500 mg twice a day. The patients in group B, who were under sequential therapy regimen, for five days received omeprazole 20 mg twice a day and amoxicillin 1 g twice a day; in the next five days, they received levofloxacin 250 mg twice a day, omeprazole 20 mg twice a day, and tinidazole 500 mg twice a day. Four weeks after the end of the therapy regimen, the patients

were visited by a doctor and using H. pylori Stool Antigen (HpSA), a test was performed to prove the eradication of H. pylori. The patients were informed about the time of HpSA test in advance and they were warned not to take proton-pump inhibitors (25-27), antibiotics, and bismuth before the test. If the patients were forced to take any medication within two weeks before the test, the patient would have been asked to notify the research team to schedule a new date for performing HpSA test.

**Ethical issues**

1) The research followed the tenets of the Declaration of Helsinki; 2) informed consent was obtained, and 3) the research was approved by the ethical committee of Shahrekrod University of Medical Sciences (Ethical code#IR.SKUMS.REC.1394.71).

**Statistical analysis**

Data collection was conducted through using a questionnaire which collected demographic data including age, sex, and education level and recorded the results of HpSA test. Analysis of the data was performed using SPSS version 18. Continuous quantitative variables were analyzed using T test and qualitative variables were analyzed using chi-square test.

## Results

Of all the patients, three patients in group A and one patient in group B were excluded from the study; as a result, the remaining 96 patients were randomly assigned to the two groups receiving sequential therapy regimen with levofloxacin (49 patients) and triple therapy regimen (47 patients). The mean age of the patients in the sequential therapy group and triple therapy group was 33.29 ± 1.54 years and 45.53 ± 2.17 years, respectively. There was a significant difference between the two treatment groups in terms of the mean age (p = 0.00). However, there was no significant difference between the two treatment groups in terms of patients' sex distribution (p = 0.57). Moreover, there was also a significant difference between the two treatment groups in terms of the distribution of patients in different education groups (p = 0.00). Table 1 presents the data on patients' age, sex, and education level.

Of the patients in the two groups, 67.3% of the patients in the sequential therapy group and 66% of the patients in the triple therapy group had negative HpSA (H. pylori Stool Antigen); there was no significant difference between the two treatment groups in terms of the eradication of H. pylori (p = 0.99) (Table 2). In addition, concerning the side effects of the medications, one person (2%) in the sequential therapy group (because of the nausea caused

**Table 1: Demographic data of patients in the two treatment groups receiving triple therapy regimen and sequential therapy regimen to eradicate H. pylori**

| Treatment Group | Sex | Number | Percentage | | P value |
|---|---|---|---|---|---|
| Sequential | Male | 23 | 46.9 | | 0.57 |
| | Female | 26 | 53.1 | | |
| Triple | Male | 22 | 46.8 | | |
| | Female | 25 | 53.2 | | |
| Sequential | 40 years and younger | 37 | 75.5 | 33.29 ± 10.7 | 0.00 |
| | Over 40 years | 12 | 24.5 | | |
| Triple | 40 years and younger | 18 | 38.3 | 45.53 ± 14.9 | |
| | Over 40 years | 29 | 61.7 | | |
| Sequential | Lower than high school diploma | 16 | 32.7 | | 0.00 |
| | High school Diploma | 18 | 36.7 | | |
| | Academic education | 15 | 30.6 | | |
| Triple | Lower than high school diploma | 34 | 72.3 | | |
| | High school Diploma | 9 | 19.1 | | |
| | Academic education | 4 | 8.5 | | |

* P < 0.05 is considered as significant.

by amoxicillin) and one person (2.1%) in the triple therapy group (because of the cramps caused by clarithromycin) were unable to tolerate the drug. However, the rest of the participants in this study did not report any treatment-specific complaints.

The results of stool antigen test were used to assess the effects of patients' age on the efficacy of sequential therapy and triple therapy for the eradication of H. pylori. The results showed that when comparing the patients aged 40 years and younger between the two treatment groups, there was no significant difference between them in terms of the treatment outcome (p = 0.32); however, when comparing patients aged over 40 years, there was a significant difference between the two treatment groups in terms of response to treatment. Accordingly, the response to treatment was better in the triple therapy group (p = 0.045) (Table 3).

The effects of education levels on eradication of H. pylori were assessed; according to the results, the responses to the treatment in sequential therapy group were significantly different between different education groups (p = 0.01), but in the triple therapy group there was no significant difference between different education groups in terms of the response to treatment (p = 0.46) (Table 4). There was a significant difference between the two groups of patients with education levels lower than high-school diploma and academic education in terms of response to treatment (p = 0.048). There was also a slightly significant difference between the two groups of patients with high-school diploma and academic education in terms of response to treatment (p = 0.063). However, there was no significant difference between the two groups of patients with an education level lower than high school diploma and with high school diploma in terms of response to treatment (p = 0.89).

**Table 2: Comparison of the results of stool antigen test between the two treatment groups receiving triple therapy regimen and sequential therapy regimen to eradicate H. pylori**

| Group Therapy | Stool antigen test (Stool Ag) | Number | Percent | P value |
|---|---|---|---|---|
| Sequential | Positive | 15 | 30.6 | 0.99 |
| | Negative | 33 | 67.3 | |
| | Drug intolerance | 1 | 2 | |
| Triple | Positive | 15 | 31.9 | |
| | Negative | 31 | 66 | |
| | Drug intolerance | 1 | 2.1 | |

*** p < 0.05 is considered as significant.**

**Table 3: Comparison of the effects of patients' age on the efficacy of treatment (based on the results of stool antigen test) between the two groups receiving triple therapy regimen and sequential therapy regimen to eradicate H. pylori**

| Group Classification | Group Therapy | Stool antigen test | | Drug intolerance | P value |
|---|---|---|---|---|---|
| | | Positive | Negative | | |
| 40 years and younger | Sequential | 7 | 29 | 1 | 0.32 |
| | | 18.9% | 78.4% | 2.7% | |
| | Triple | 6 | 11 | 1 | |
| | | 33.3% | 61.1% | 5.6% | |
| Over 40 years | Sequential | 8 | 4 | | 0.045 |
| | | 66.7% | 33.3% | | |
| | Triple | 9 | 20 | | |
| | | 31% | 69% | | |

*** p < 0.05 is considered as significant.**

**Table 4: Comparison of the effects of patients' education on the efficacy of treatment (based on the results of stool antigen test) between the two groups receiving triple therapy regimen and sequential therapy regimen to eradicate H. pylori**

| Treatment Group | Education level | Stool antigen test (stool Ag) | | Drug intolerance | P value |
|---|---|---|---|---|---|
| | | Positive | Negative | | |
| Sequential | Lower than high school diploma | 9 | 17 | 0 | 0.01 |
| | | 56.3% | 43.8% | 0% | |
| | High school diploma | 5 | 12 | 1 | |
| | | 27.8% | 66.7% | 5.6% | |
| | Academic education | 1 | 14 | 0 | |
| | | 6.7% | 93.3% | 0% | |
| Triple | Lower than high school diploma | 9 | 24 | 1 | 0.46 |
| | | 26.5% | 70.6% | 2.9% | |
| | High school diploma | 5 | 4 | 0 | |
| | | 55.6% | 44.4% | 0% | |
| | Academic education | 1 | 3 | 0 | |
| | | 25% | 75% | 0% | |

* $p < 0.05$ is considered as significant

**Table 5: Comparison of the effects of patients' sex on the efficacy of treatment (based on the results of stool antigen test) between the two groups receiving triple therapy regimen and sequential therapy regimen to eradicate H. pylori**

| Treatment Group | Sex | Number | Percentage | P value |
|---|---|---|---|---|
| Sequential | Male | 23 | 46.9 | 0.009 |
| | Female | 26 | 53.1 | |
| Triple | Male | 22 | 46.8 | 0.64 |
| | Female | 25 | 53.2 | |

The effect of sex on eradication of H. pylori was also assessed. In the triple therapy group, there was no significant difference between females and males in terms of response to treatment ($p = 0.64$); however, in the sequential therapy group, a significant difference was observed between females and males in terms of response to treatment ($p = 0.009$). Accordingly, the response to treatment was better in males than females in the sequential therapy group (Table 5).

## Discussion

This study was conducted to compare standard triple therapy regimen with sequential therapy regimen containing levofloxacin used for the eradication of H. pylori in patients with gastrointestinal infection caused by H. pylori. H. pylori eradication rate was 67.3% in the sequential therapy regimen and 66% in standard triple therapy regimen. As the main goal of treatment is to eradicate the infection in 85-95% of the patients; however, because of the lower treatment success rates observed in this research, hence, these two regimens in this study is not recommended.

Several studies have been conducted on standard triple therapy in Iran. In a study by Aminian and colleagues, the regimen consisted of omeprazole 20 mg twice a day, amoxicillin 1 g twice a day, and clarithromycin 500 mg twice a day which had been administered for 10 days with the eradication rate of 90.7% [30]. Moreover, Keshavarz and colleagues used the above-mentioned treatment regimen for seven days and reported an eradication rate of about 87.5% [31].

Furthermore, one of the most common causes of treatment failures could be the emergence of new antibiotic-resistant bacterial strains [32]. In this study, the emergence of H. pylori strains resistant to the antibiotics might have been a cause of treatment failure. In a similar study conducted by Polat and colleagues, of a total of 72 patients receiving

sequential regimen containing levofloxacin, 65 patients were affected by gram-negative bacteria, while of a total of 67 patients receiving standard triple therapy regimen, only 34 patients were affected by gram-negative bacteria [29], which may refer to the fact that in different geographic areas, bacterial resistance to antibiotics might be different.

Because of the common complication of furazolidone and high cost of clarithromycin, many Iranian physicians routinely prefer to use metronidazole, amoxicillin, bismuth, and omeprazole for H. pylori eradication [4]. In this study, the patients in triple therapy for ten days received omeprazole 20 mg twice a day, amoxicillin 1 g twice a day, and clarithromycin 500 mg twice a day; however, the patients in the sequential therapy group for five days received omeprazole 20 mg twice a day and amoxicillin 1 g twice a day; in the next five days, they received levofloxacin 250 mg twice a day, omeprazole 20 mg twice a day, and tinidazole 500 mg twice a day. In fact, H. pylori resistance to these antibiotics might have been a reason for reduced efficacy of the regimens in eradication of the bacterial infection in this research. Long-term clarithromycin monotherapy for the treatment of respiratory tract diseases could indeed lead to the increased resistance to this antibiotic. H. pylori resistance to clarithromycin might also be the most important factor explaining the failure of treatment regimens, particularly triple therapy, used for the eradication of infection [33-36]. Moreover, it is reported that the optimal efficacy of metronidazole-based triple and quadruple drug regimens in western countries is about 80-95% [5, 15]. However, due to the high rates of resistance to metronidazole in Iran [37,38], the eradication rate is usually not optimal [4, 39]. In this study, the use of the mentioned treatment regimens may have resulted in low rates of H. pylori eradication which is consistent with the findings of Zhou and colleagues' study (in 2014) who reported the H. pylori resistance to sequential and triple therapy regimens [40].

Studies which have compared sequential and triple therapy regimens have reported different results, as some of them reported the superiority of sequential treatment regimen while other others have reported the superiority of triple therapy regimen [32, 41-44]. In a study conducted by Khaleghi and colleagues, the patients with chronic dyspepsia were classified into two groups each consisting of 80 people [45]. One of the groups received omeprazole and amoxicillin for the first five days and then omeprazole, furazolidone, and clarithromycin for the next nine days; the other group received quadruple regimen for 14 days consisting of omeprazole, amoxicillin, clarithromycin, and bismuth. Of all, 50.9% of the patients in the sequential therapy group and 49.1% of the patients in the second group were cured, and the difference was not statistically significant [45]. In another study, Kaboli and colleagues investigated 140 patients with dyspepsia and classified them into two groups; the first group received omeprazole, amoxicillin, and clarithromycin for 14 days and the second group (sequential group) first received omeprazole and amoxicillin for five days, and then omeprazole, clarithromycin, Tinidazole for the next five days; there was no significant difference between the two groups in terms of H. Pylori eradication [46]. Zullo and colleagues studied 36 patients who received rabeprazole 20 mg twice a day, levofloxacin 250 mg twice a day, and amoxicillin 1 g twice a day. According to the results, H. pylori was successfully treated in 30 patients [47]. In fact, comparing with the sequential regimen used in this study and the obtained results, it can be concluded that the H. pylori strains resistant to levofloxacin might have been caused by the indiscriminate use of antibiotics in this region.

In the present study, considering people in the age group over 40 years, the eradication rate in the triple therapy group (69%) was higher than the eradication rate in the sequential therapy group (33.3%) ($p = 0.045$). To justify these results, it can be concluded that the use of sequential therapy regime, especially for older people, is more difficult than that of triple therapy regimen. The more complex schedule for taking sequential therapy regimen, especially in people over 40 years of age, may increase the risk of treatment failure in this study. Nevertheless, Hashemi and colleagues (in 2007) reported that patients' age had no significant relationship with the eradication of H. pylori [4]. Higher education level is reported as a factor influencing the eradication of H. pylori infection. In this study, the highest level of eradication was observed in people with an academic degree. These findings are in line with other studies in this field that have proven H. pylori infection is lower among people with higher education levels [48-50]. People with lower education level are indeed at a higher risk of infection than those with higher education levels; such a negative relationship is also observed between parents' education and infection [51,52].

The results of this study showed that men had a better response to treatments than women. It is inconsistent with the results of studies by Misattari and Hashemi which reported no statistically significant difference between men and women in terms of the response to treatments; however, in this study in patients in the triple therapy group, there was no significant difference between the two sexes in terms of response to treatments [4, 32, 53].

Given the low rate of H. Pylori eradication by the sequential and triple therapy regimens observed in this study, further research must be conducted to study the resistance of the bacteria to the studied treatment lines and antibiotics in Iran. Considering the results of this study, it is also recommended to utilize other treatment regimens to achieve higher rates of eradication. It is also suggested to use more effective and simple treatment regimens for older people and those with lower education levels.

## Conclusion

The use of sequential therapy regimen containing levofloxacin for the eradication of H. pylori results in outcomes which are less than the optimal levels. However, further studies in this field are needed to be carried out with larger sample size in different places.

**Acknowledgments**
This study was extracted from M.D thesis of Kian Kaveh-Zadeh (Thesis #1214).

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