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Sequential Therapy versus Standard Triple Therapy for Helicobacter Pylori Eradication in Iran: a double-blind, randomized, placebo-controlled trial

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Abstract

Background and aim: Currently, different regimens are used for Helicobacter pylori eradication. The aim of this study is to compare the efficacy and safety of sequential and standard triple therapy for Helicobacter pylori eradication in Bandar Abbas in 2018.

Methods: This randomized controlled trial was done on 150 patients in Bandar Abbas in 2018. Patients were randomly assigned into two groups either to receive standard triple therapy or sequential therapy for Helicobacter pylori eradication. Patients were followed for helicobacter eradication, minor and major side effects and drug intolerance. Data were analyzed using SPSS 23.0 software.

Results: Two groups were similar in baseline characteristics. Helicobacter pylori eradication was reported in 70 (90.9 %) in the sequential and 54 (74 %) in the standard triple therapy group (p=0.006). Minor side effects were reported in 20 (26 %) in the sequential and 36 (49.3 %) in the standard triple therapy (p=0.003). Major side effects (p=0.142) and drug intolerance (p=0.480) were similar in both groups.

Conclusion: Sequential therapy is more effective and has lower rate of minor complications in eradication of Helicobacter pylori.

Trial registration: The protocol of study was registered at the Iranian Registry of Clinical Trials (IRCT) with ID number of IRCT20180131038581N2.

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Keywords: Helicobacter pylori, Sequential therapy, Triple therapy

Note: This study has followed the CONSORT Statement, which is an evidence-based, minimum set of recommendations for reporting randomized trials. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation.

1. Introduction

1.1. Background

Helicobacter pylori (H. pylori) is a gram negative, highly mobile and slow-growing, spiral bacterium. Nearly half of the world's population is infected with this infection (1). Its prevalence in Saudi Arabia is about 51-78% (2-5). Among the complications of this infection are chronic stomach inflammation, duodenal ulcer, gastric cancer, or gastric malt lymphoma (6). Treatment can improve digestion, gastric ulcer and malt lymphoma, and can also prevent

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gastric cancer progression (7). The proposed treatment for H. pylori infection is a three-dose regimen consisting of a Proton-pump inhibitor (PPI), clarithromycin and amoxicillin or metronidazole for 7-14 days (8). Recent reports have shown that the success rate of the standard triple therapy worldwide has declined due to increased resistance to clarithromycin or metronidazole (9). A study in Saudi Arabia reported resistance rates in subjects with metronidazole 80%, clarithromycin 4%, amoxicillin 1.3%, and tetracycline 0.4% (10). H. pylori diagnostic tests include the urease test on a biopsy specimen, a rapid urease test, a histological study, as well as serological serum tests and fecal antigen. One of the most accurate methods for confirming the presence of H. pylori is the urease test on the biopsy specimen. Different antibiotics for the treatment of H. pylori have been investigated (11-15). However, few have succeeded in eradicating it. Drug resistance information is also insufficient for use in treatment. The most widely used drug treatment examines some issues such as drug resistance, antibiotic use and allergy to some species, price, complications, and ease of use.

1.2. Statement of problem

There is no new drug for the treatment of this infection. Thus, researchers use successful alternative therapies, such as the combination of antibiotics and sequential therapies (9). Sequential therapy for 10 days is 5 days of PPI treatment plus an antibiotic (usually one gram of amoxicillin twice daily) followed by 5 days of treatment with PPI plus two other antibiotics (usually clarithromycin and tinidazole / metronidazole). A recent meta-analysis showed that ten-day sequential therapy was more effective than the standard treatment of three-to-seven-day medicines for the eradication of H. pylori infection (93.4% for sequential treatment versus 76.9% for standard triple therapy) (16). The duration of treatment with PPI seems to increase the recovery rate (17). Precise information on the more effective treatment of this infection in Iran is not available, so the aim of this study was to compare sequential treatment with triple therapy to eradicate H. pylori infection.

1.3. Objectives

The general objective of this study was to compare the efficacy of eradication of H. pylori infection by using sequential therapy and triple therapy in patients with this infection referring to the public and private sectors of Bandar Abbas gastroenterology in 2018.

2. Material and Methods

2.1. Participants and research design

The study was a double-blinded randomized controlled trial carried out in Shahid Mohammadi Hospital, Bandar Abbas (Iran) in 2018. To reach the desired sample sized, all patients with H. pylori infection who had the inclusion criteria were included in the study using convenient sampling. Considering the power of 80% and confidence interval of 95% and an equal number of participants in each group and assuming 70% and 90% H. pylori eradication in standard triple therapy and sequential group, a sample size of at least 72 patients in each group was calculated (18). Considering the possibility of loss of follow-up, 150 patients were included in the study (Figure 1). Samples were collected using convenient sampling method.

2.2. Selection criteria

2.2.1. Inclusion criteria

Patients who had not previously been treated for H. pylori and were older than 18 years of age.

2.2.2. Exclusion criteria

Pregnant or lactating patients, patients with severe heart, kidney, lung, or liver disease, patients with malignancies, and patients who were allergic to amoxicillin, clarithromycin, or tinidazole. Also, patients who did not consent to participate in the study were excluded.

2.3. Data collection tool

A questionnaire was filled out for all patients disclosing age, sex, and type of referral (nausea, vomiting, weight loss, dyspepsia, melena and hemoptysis, etc.).

2.4. Randomization and blinding

This was a randomized double-blind clinical trial. Patients were randomly divided into two groups of sequential therapy and standard triple therapy using a computerized randomization system. Information about the type of treatment was kept secret from pathologists and physicians involved in the treatment. For this purpose, the drugs of each group were placed in identical packages alongside the instructions and were given to the patients.

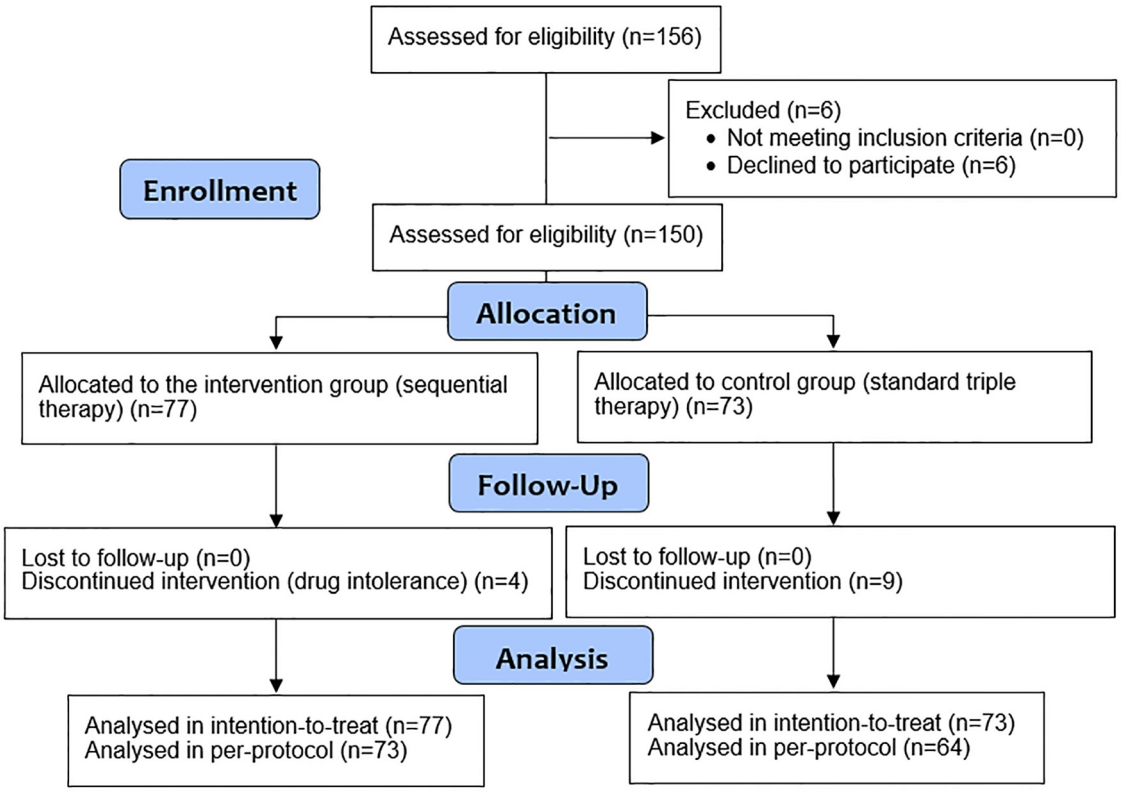

Figure 1. CONSORT 2010 diagram of the clinical trial

2.5. Procedure

This study was a randomized controlled trial. Those with gastrointestinal symptoms such as nausea, vomiting, indigestion and melena, who did not respond to experimental PPI therapy and who were candidates for endoscopy, were included in the study. In this study, patients with H. pylori infection at the Shahid Mohammadi Hospital of Bandar Abbas in 2018 underwent gastroscopy. Initial H. pylori diagnostic tests in these patients are biopsy, rapid urea test, and histological evaluation. Of all the patients who underwent esophago-gastro-duodenoscopy, three biopsy samples were taken from the intrum, incisura, and stomach trunk. Intramuscular tissue was used for rapid urea test (RUT). Histological evaluation was used for body and incisura. Patients who had this organism in their RUT were considered as being infected with H. pylori. Patients in the sequential therapy group received pentaprazole 20 mg twice daily for 10 days, amoxicillin 1000 mg twice daily for the first 5-day period followed by tinidazole 500 mg twice daily for the second 5-day period. Patients in the standard triple therapy group, received pentaprazole 20 mg, clarithromycin 500 mg, and amoxicillin 1000 mg (all medicines twice daily) for 14 days. The medications were kept in similar boxes and had codes, and patients and outcome assessors were unaware of the treatment allocations. Negative urea breath test (UBT) results four weeks after the completion of treatment were considered as H. pylori eradication. Patients should avoid taking PPI and bismuth for 2 weeks and antibiotics for at least 4 weeks prior to UBT. The primary outcome of the study was H. pylori eradication and secondary outcomes were drug side effects and drug intolerance. The results of the treatment were evaluated by interpreting the results of the UBT test as well as the symptoms of the patient and checking the side effects of the medicine by the gastroenterologist. Then the results of the therapy were entered into a premade checklist. Drug side effects are divided into three categories:

- Mild drug side effects: The severity of the side effects is such that with the diagnosis of the doctor it is possible to continue the treatment.
- Severe drug side effects: Side effects are so severe that the doctor decides the drug taking should be discontinued.
- Drug intolerance: Drug side effects for which the physician has not indicated the discontinuation of the medication, but the patient has interrupted the drug due to intolerance to the side effects.

2.6. Data analysis

After collecting the information and completing all stages, the data were analyzed by IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA), using descriptive statistics (mean, standard deviation and percentage), Chi-square test. P-value <0.05 was considered as the significance level for this study. Intention-to-treat and per-protocol methods were used to analyze the data. In the first method, the patients were put into groups based on the first randomized event and eventually were analyzed. In the second method, only those who completed the course of their treatment according to the protocol were analyzed.

2.7. Ethics

All the procedures in this study were in conformity with the Declaration of Helsinki and were approved by the local Human Research Ethics Committee. The study is approved by the Ethical Committee of Hormozgan University of Medical Sciences (Ref: HUMS.REC.1396.123). The trial was registered in the Iranian Clinical Trial Registration Center (IRCT registration ID: IRCT20180131038581N2). A written informed consent was obtained from all patients before participating in the study and undergoing esophago-gastro-duodenoscopy.

3. Results

3.1. Demographic results

In this study, 150 patients were investigated. Of the subjects, 77 patients (51.3%) were in the sequential therapy group and 73 (48.7%) were in the standard triple therapy group. Seventy-six subjects (50.7%) were male and 74 (49.3%) were female. Nausea was reported in 50 patients (33.3%), vomiting in 79 patients (46.7%), indigestion in 143 patients (95.3%) and melena in 5 patients (3.3%). None of the patients in this study had weight loss. The mean age of the subjects was 35.77±9.37 years.

3.2. Main results

3.2.1. Comparison of baseline characteristics of patients in two groups

In Table 1, two groups were compared in terms of baseline characteristics. Based on the results of this table, the two groups did not differ statistically regarding baseline characteristics.

3.2.2. Comparison of the main results of the study in two groups using Intention-to-Treat method

The results of comparison of H. pylori eradication in the two groups using intention-to-treat method are presented in Table 2. Based on the results of this study, in the sequential therapy group, successful eradication in 70 patients (90.9%) and in the standard triple therapy group, successful eradication for 54 (74%) patients was reported (p=0.006).

Table 1. Comparison of baseline characteristics between the sequential therapy and standard triple therapy groups

Variable		Sequential group	Standard triple group
Age (year)		29.36 ± 9.46	35.21 ± 9.20
Sex	Male	38 (49.4 %)	38 (52.1 %)
	Female	39 (50.6 %)	35 (47.9 %)
Nausea		34 (44.2 %)	24 (32.9 %)
Vomiting		29 (37.7 %)	38 (52.1 %)
Indigestion		75 (97.4 %)	68 (93.2 %)
Melena		1 (1.3 %)	4 (5.5 %)

Table 2. Comparison of H. pylori eradication success in two groups using intention-to-treat method and per-protocol method

Comparisons		Sequential therapy group		Standard triple therapy	p-value*
H. pylori Eradication	Intention-to-treat method	Yes	70 (90.9%)	54 (74%)	0.006
		No	7 (9.1%)	19 (26%)	
	Per-protocol method	Yes	70 (95.9%)	52 (81.3%)	0.006
		No	3 (4.1%)	12 (18.8%)	

* Chi-square test

3.2.3. Comparison of the main results of the study in two groups using Per-Protocol method

The results of comparison of H. pylori eradication in the two groups using per-protocol method are presented in Table 2. Based on the results of this study, in the sequential therapy group, successful eradication in 70 patients

(95.9%) and in the standard triple therapy group, successful eradication in 52 (81.3%) patients was reported (p=0.006).

3.2.4. *Comparison of mild side effects in two groups*

The results of the study showed that in the sequential therapy group, 20 patients (26%) had mild side effects. This rate was 36 patients in the standard triple therapy group (49.3%). The difference was statistically significant. The details of this comparison are presented in Table 3.

3.2.5. *Comparison of severe side effects in two groups*

The results of the study showed that in the sequential therapy group, 3 patients (3.9%) and in the standard triple therapy group, 7 patients (9.6%) had severe side effects. The difference between the groups was not statistically significant (p=0.142). The details of this comparison are presented in Table 3.

3.2.6. *Comparison of drug intolerance in two groups*

Based on the results of the study, drug intolerance was observed in one patient (1.3%) in the sequential therapy group and in two patients (2.7%) in the standard triple therapy group (Table 4). The difference between the groups was not statistically significant (p=0.480).

Table 3. Comparison of mild and severe side effects in two groups

Side effects	Sequential therapy group		Standard triple therapy	p-value
Minor side effects	Yes	20 (26%)	36 (49.3%)	0.003*
	No	57 (74%)	37 (50.7%)	
Major side effects	Yes	3 (3.9%)	7 (9.6%)	0.142*
	No	74 (96.1%)	66 (90.4%)	

* Chi-square test

Table 4. Comparison of drug intolerance in two groups

	Sequential therapy group		Standard triple therapy	p-value
Drug intolerance	Yes	1 (1.3%)	2 (2.7%)	0.480*
	No	76 (98.7%)	71 (97.3%)	

* Chi-square test

4. Discussion

In this study, two methods of eradicating H. pylori were compared. The common method is the standard triple therapy. This method, although commonly used by general practitioners and gastroenterologists, has been shown to cause some difficulties and intolerance in some patients due to side effects. In addition, not only do newer regimens appear to be more effective in eradicating H. pylori, but also, they are better tolerated by the patient and have fewer side effects. In this study, the primary aim was to study the success rate of the two therapy methods in eradicating H. pylori, which was confirmed by urease test. For this purpose, two methods were used. The first is intention-to-treat, in which patients are examined based on the primary grouping. The second method is per-protocol, in which patients who have completed the treatment protocol are analyzed. In the study, based on the intention-to-treat method, 90.9% successful eradication in the sequential group and 74% successful eradication in the standard triple therapy group were observed. Also, based on the per-protocol method, 95.9% successful eradication in the sequential group and 81.3% successful eradication in the standard triple therapy group were observed. In both methods, the sequential therapy was superior to and more effective than standard triple therapy in eradicating H. pylori. One of the treatments that has recently been taken into consideration by the researchers is the sequential therapy regimen. This regimen has been shown to be more effective in several studies than standard triple therapy, and it seems to be associated with fewer complications and side effects in patients. It seems that patients have more compliance with this regimen. This superior effectiveness of sequential therapy has been confirmed by several other studies. In a study by Seddik et al., which was conducted on 281 people, it was shown that the therapeutic efficacy of the sequential method is greater than standard triple method using both intention-to-treat method and the per-protocol method (18). The percentage of eradication of H. pylori in the standard triple therapy was 65.9% and 71% in the intention-to-treat and per-protocol methods respectively, and was 82.8% and 89.9% in the sequential therapy group in intention-to-treat and per-protocol methods respectively. In this study, as in our study, the superiority of the sequential therapy method to the standard triple therapy has been shown. In another study by Nasa et al. in 2013, the percentage of eradication of H. pylori by sequential therapy method was 81.8% versus 42.4% in the standard triple therapy group using per-protocol method (19). In the intention-to-treat analysis, these percentages were 88.2% versus 79.1%, respectively. These results are almost the same as our study. In another study, Lahbabi et al. showed

that sequential therapy had 94.2% and 96% successful eradication rate using intention-to-treat and per-protocol analysis respectively (20). In this study, like our study, it was shown that the sequential therapy method in comparison with other methods had better efficacy. In a study by Vaira et al. in 2007, it was shown that in the intention-to-treat analysis, H. pylori eradication was 89% and 77% in the sequential therapy method versus the standard triple therapy method respectively (21). Also, in per-protocol analysis, H. pylori eradication was 93% and 79% in the sequential therapy method versus the standard triple therapy method respectively. This study also confirms the results of our study.

In a 2016 study, Nyssen et al. compared the H. pylori eradication effects of sequential therapy and standard triple therapy using meta-analysis (22). The results of this study showed that prior to 2008, studies clearly demonstrated the superiority of the sequential therapy method in eradication of H. pylori, but this advantage has been reduced in recent results. The superiority of the sequential therapy method is more pronounced when the 7-day period is used instead of the 10-day period of standard triple therapy method. Despite the fact that studies often indicate the superiority of the sequential therapy method to the standard triple therapy method, several points should be taken into consideration. As noted in the Nyssen study (22), this superiority is more observed in older studies, and the change in H. pylori drug resistance pattern may lead to changes in this issue. Also, although many studies have shown the superiority of the sequential therapy method to the standard triple therapy method, in most studies, the success rate of sequential therapy is less than 90%, which makes it impossible to treat this method as a replacement for the standard triple therapy method.

In the present study, the two groups did not differ significantly in terms of severe side effects and drug intolerance. However, 26% in the sequential therapy group and 49.3% in the standard triple therapy group experienced mild drug side effects. The mild side effects in sequential therapy groups were significantly lower compared to those of the standard triple therapy group. In the study of Seddik et al. (18), drug intolerance was not significantly different in the two groups, and in the case of drug side effects, the prevalence in the sequential therapy group and the standard triple therapy group was 27.5% and 27.9%, respectively with no statistically significant difference. In this regard, the results were different from those of our study. In the study of Nasa et al., unlike our study, the prevalence of side effects was not significantly different between the two groups, and was 23.5% and 14.6% in the sequential therapy group and the standard triple therapy group, respectively (19). In the study of Lahbabi et al. similar to our study, the prevalence of drug side effects in the sequential therapy group was 6.9% which was significantly lower than the standard triple therapy group (20). The study of Vaira et al. mentioned the incidence of drug side effects by 17% in each group, which was not statistically significant and is contradictory with our study results (21). Also, one patient in the standard triple therapy group discontinued his/her therapy. In our study, one patient in the sequential therapy group and two patients in the standard triple therapy group discontinued their therapy.

The results of studies on drug side effects and drug intolerance are very different. Although it seems that the prevalence of mild drug side effects in our study groups, especially the standard triple therapy group, was high (about half of the patients), the cause of this issue could be due to different definitions of drug complications and side effects. In the present study, patients were asked at the time of follow-up on the presence or absence of mild drug side effects. This might have affected their answers and it is possible that they answered positively despite the fact that complications and side effects were not truly a complaint of them.

5. Limitations

One of the limitations of this study was the discontinuation of medication by the patient or physician, which caused the patients not to receive the desired medication dosage. Failure to receive the drugs by patients can result in bias in the study results. In order to solve this problem, the data have been analyzed using two methods: intention-to-treat and per-protocol. Among other limitations of this study that can be noted is that patients were asked about drug complications in order to evaluate the mild side effects of drugs. This could draw their attention too much to the side effects of the drug, so that they reported the presence and severity of these side effects higher than the actual level.

6. Conclusions

The use of sequential regimen in the eradication of H. pylori is associated with a higher efficacy and fewer side effects than the standard triple regimen. Therefore, using of this method is recommended for the eradication of H. pylori. Considering the results of this study and similar studies, the sequential therapy method has better efficacy and less complications compared to the standard triple therapy. Thus, it is recommended that this method be used to

eradicate H. pylori. However, this treatment requires other studies over time, and other treatment regimens may have similar or better efficacy.

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Conflict of Interest:
There is no conflict of interest to be declared.

Authors' contributions:
All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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