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A comparison between standard triple therapy and sequential therapy for *Helicobacter pylori* eradication in patients with dyspepsia: A randomized clinical trial

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RESEARCH ARTICLE

ABSTRACT

Introduction:

Helicobacter pylori is a common infectious agent and the main cause of gastro-duodenal disorders. The present study aimed to compare the two methods of sequential therapy and standard triple therapy (STT) for the eradication of *Helicobacter pylori*.

Patients and Methods:

In this study, 191 patients with *H.pylori* and over the age of 18 years were randomized into two groups. They received either STT (Omeprazole 20mg capsules twice a day, Amoxicillin 1g capsules and Clarithromycin 500mg capsules twice a day for 14 days) or sequential therapy (Omeprazole 20mg capsules twice a day and Amoxicillin 1g capsules twice a day for the first week and Omeprazole 20mg capsules twice a day, Clarithromycin 500mg capsules twice a day, and Metronidazole 500mg tablets twice a day for the second week).

Results:

The eradication rates of *H.pylori* infection in sequential therapy based on the analysis of intention to treat (ITT) and per protocol (PP) were 73% and 76% respectively. The eradication rates in triple therapy were 65% and 68.4% respectively. There was no statistically significant difference between the groups (P>0.05).

Conclusion:

The findings showed that there is no significant difference between the two methods of sequential therapy and triple therapy for *H.pylori* eradication. Future studies with larger sample sizes can be useful in choosing one of the two methods.

Keywords:

Helicobacter pylori; sequential; triple therapy; Iran

1. INTRODUCTION

Helicobacter pylori is a common infectious agent and the main cause of gastro-duodenal disorders. This infection leads many digestive disorders, such as chronic gastritis, peptic ulcer disease, upper gastrointestinal bleeding (UGIB), MALToma, chronic atrophic gastritis, intestinal metaplasia, and gastric adenocarcinoma [1, 2 ,3].

Standard triple therapy (STT), consisting of proton pump inhibitor (PPI), Clarithromycin, and either Amoxicillin or Metronidazole, has been represented as a golden standard and is the first-line therapy for eradication of *Helicobacter pylori* [4,5]. It has a high success rate of 80%, acceptable safety standards, and the process is relatively simple. But, increasing resistance to Clarithromycin and Metronidazole in the last decade has led to reduced effectiveness (less than 80%) of this therapy [5, 6,7].

In recent years, the sequential regimen has been largely used. Its eradication rate for *H.pylori* infection is 90–94% [8,9,10]. This two-step treatment includes the use of a PPI and amoxicillin over the first seven days of treatment, and PPI together with Clarithromycin and Tinidazole or Metronidazole over the next seven days. This has better efficiency compared with STT [9-12]. The present study aimed to compare the two methods of sequential therapy and STT for the eradication of *H.pylori* in patients with dyspepsia.

2. PATIENTS AND METHODS

The present study was a randomized clinical trial conducted in the gastroenterology clinic of Shohada-ye-Ashayer Hospital, (Lorestan province, in West of Iran) between July 2015 and January 2016. At the beginning of the study, adequate explanations were made to the patients about its design. No threats were made to them to participate in the project. All eligible participants signed an informed consent letter. They had the right to opt out of the study any time. They were also assured that all information would be confidential. The Ethics Community of the Lorestan University of Medical Science, Khorramabad, Iran, approved of the study. The

study was registered in the Iranian Registry of Clinical Trials (IRCT2015082323736N1). Randomization was done by assigning random numbers to each subject. The patients were randomized (by a ratio of 1:1) and divided into two (even and odd) groups using a computer. One of the codes, A or B, was assigned to each patient. Code A was for the sequential therapy group and Code B was for the triple therapy group.

2.1. Inclusion criteria

Patients over the age of 18 years, who have dyspepsia, who are undergoing endoscopy, and whose biopsy specimen has been confirmed for *H.pylori* infection based on histology, were enrolled into the study.

2.2. Exclusion criteria

(a). Patients with a previous history of *H.pylori* eradication (b).Pregnant or lactating women (c).Those with a history of allergy to drugs used for eradication (d). Patients under the age of 18 years (e). History of gastric surgery (f). Patients with chronic renal failure and liver cirrhosis.

The eligible patients were randomly assigned to one of the treatment groups of the study. Group A: Sequential therapy regimen (Omeprazole 20mg twice a day and amoxicillin 1g twice a day for the first week and Omeprazole 20mg twice a day, Clarithromycin 500mg twice a day, and metronidazole 500mg twice a day for the second week). Group B: Standars Triple Therapy regimen (Omeprazole 20mg twice a day, amoxicillin 1g and Clarithromycin 500mg twice a day for 14 days). All patients were visited by a physician to check their drug tolerance and side effects once when they were taking the drugs and once at the end of the treatment period. All patients completed a self-administered questionnaire designed for this purpose.

2.3. Primary outcome

Six weeks after the completion of treatment, *H.pylori* eradication was evaluated in each group by urea breathe test (UBT), using PY test kits, Kimberly_Clark USA Co.

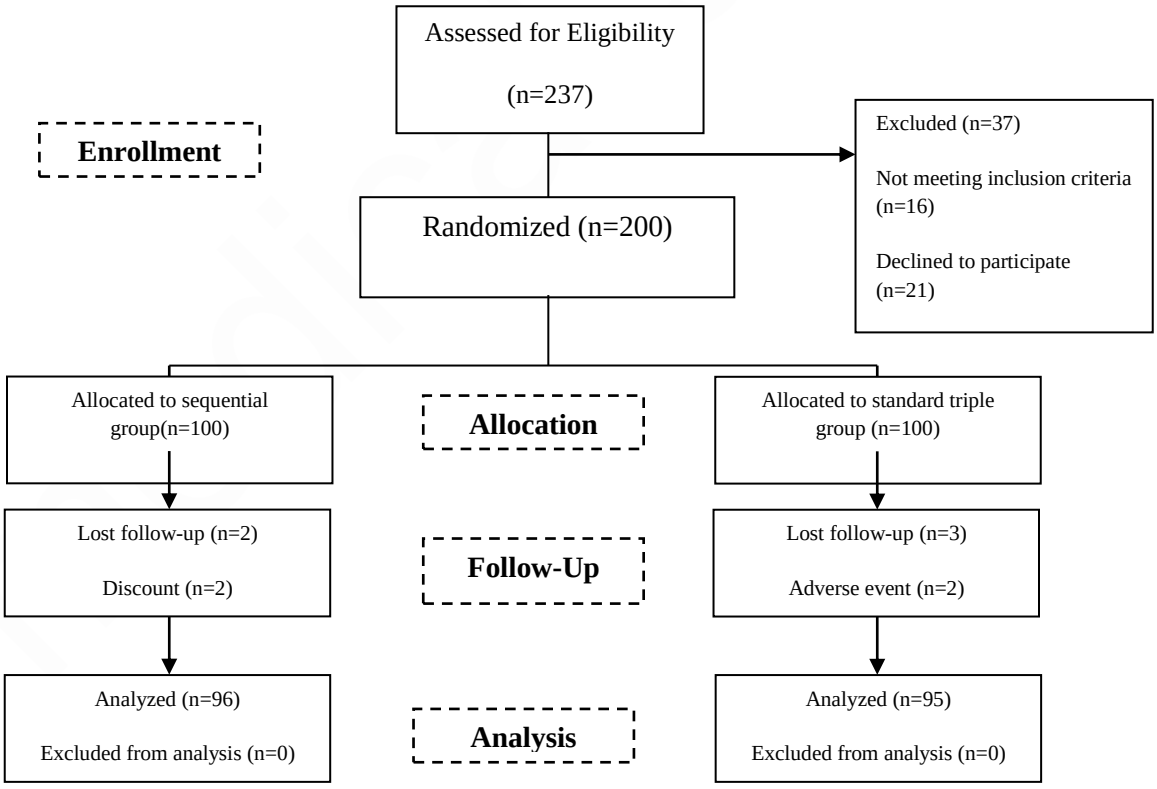

Figure 1 Flowchart of the design, groups and participants in this study

2.4. Secondary outcome

The tolerance and adherance rate in each therapeutic regimen was evaluated and common side effects of medicines were studied. Adherence is defined based on the number of the consumed pills. If the patient has consumed more than 90% of the pills, it is considered acceptable. The definitions of the side effects of drugs were based on the complications after starting the medication.

2.5. Statistical analysis

The data collection tools were questionnaires and interviews. The raw data was inserted into SPSS version 22 and descriptive statistics (mean, standard deviation, and frequencies), analytical statistics such as ANOVA (for quantitative variables), chi-square (for qualitative variables), and multiple logistic regression for the control of confounding variables. The significance level was considered at $P<0.05$.

3. RESULTS

In all, 237 dyspeptic patients were referred to the gastroenterology clinic of Shohada Ashayer Hospital. They were evaluated for their participation in the study. Sixteen people did not meet the inclusion criteria and 21 were not willing to participate. Overall, 200 patients met the inclusion criteria and agreed to participate in it. The patients were divided into two equal groups of 100 each. They were randomly assigned to the treatment groups of STT and sequential regimen based on Clarithromycin. Four people in the sequential regimen group did not complete the study (two due to severe medical complications, and two failed to follow the guidelines) and five people in the STT group were excluded from the study (three due to severe medical complications, and two failed to follow the guidelines). Finally, 191patients completed the study: 96 cases in the sequential therapy regimen c (group A) and 95 cases in the STT group (group B). The patients' selection processes are given in Figure 1.

Table 1 Demographic characteristic of the patients

	ITT		PP	
	Sequential	Triple	Sequential	Triple
Number of patients	100	100	96	95
Age(mean ±SD)years	41.9±13	41.4±12.2	43±13	41.4±12.3
≥30	20(20%)	20(20%)	19(19.8%)	19(20%)
31-40	30(30%)	34(34%)	29(30.2%)	32(33.7%)
41-50	23(23%)	18(18%)	22(22.9%)	18(18.9%)
≤ 51	27(27%)	28(28%)	26(27.1%)	26(27.4%)
sex				
Male	50(50%)	49(49%)	48(50%)	46(48.4%)
Female	50(50%)	51(51%)	48(50%)	49(51.6%)

The mean age of the patients was 42±13 years in Group A, and 41.4±12.3 years in Group B. Group A included 48 men (50%) and 48 women (50%). Group B consisted of 46 men (48.4%) and 49 women (51.6%). The demographic characteristics of the participants have been presented in Table 1.

3.1. Primary outcome

The eradication rate of *H.pylori* infection in Group A, based on the analysis of ITT and per protocol (PP) was respectively 73% and 76%, and the respective percentage in Group B was 65% and 68.4%. The results of the eradication rate of H.pylori in the two groups have been shown in the Table 2.

Based on the logistic regression test, the odds ratio of the eradication of *H.pylori* in Group A is 1.4 times more than Group B. According to the significance level of less than 0.05, this rate is not statistically significant (p=0.155). Table 2 indicates the eradication rates between the two treatment groups. Based on the ITT and PP analyses, there was no significant difference in the eradication rates between the sequential and STT groups. Overall, the eradication rate of patients in the sequential and STT groups in the ITT analysis was respectively 73% and 65%. In the PP analysis, it was respectively 76% and 68.4%. There was no significant difference in the eradication rates between the patients in the two groups.

Table 2 *Helicobacter pylori* eradication rates of triple therapy and sequential therapy

	Classic triple therapy	Sequential therapy	OR	p-value
Intention to treat	**62/95 (68.4%)**	**71/96 (73%)**	1.4	**0.155**
Per protocol	**65/100 (65 %)**	**73/100 (76%)**	1.95	**0.145**

3.2. Secondary outcomes

In Group A (n=15), 15.6% patients and in Group B (n=17), 17.9% patients experienced side effects during treatment. This number was not statistically significant for the two groups (P=0.702). The most common side effect was anorexia in Group A (9.3%) and abdominal pain in Group B (14.7%). Other side effects are presented in Table 3.

Table 3 Side effects of sequential therapy and triple therapy

Variables	Sequential therapy N (%)	Triple therapy N (%)	OR	P value
Nausea	8(8.33%)	6(6.31%)	1.34	0.399
Vomiting	2(2.08%)	2(2.1%)	0.98	0.686
Diarrhea	4(4.16%)	6(6.31%)	0.64	0.367
Abdominal pain	8(8.33%)	14(14.73%)	0.52	0.123
Constipation	3(3.12%)	2(2.1%)	1.5	0.505
Anorexia	9(9.37%)	10(10.52%)	0.87	0.490
Rash	0(0%)	1(1.05%)	0	0.497
Headache	2(2.08%)	3(3.15%)	0.65	0.495
Bad taste	7(7.29%)	10(10.52%)	0.66	0.298
Total advers events	15(15.6%)	17(17.9%)	0.92	0.702
Patients who withdrew	2(2.08%)	3(3.15%)	1.08	0.115
Adherence	96(96%)	95(95%)	1.79	0.651

4. DISCUSSION

The current study aimed to evaluate the STT (triple therapy) and sequential therapy in treating patients with dyspepsia for eradication of *H.pylori* infection. The findings of this study demonstrated that the *H.pylori* eradication rate was the same in the two groups. There was no significant difference in the eradication rate between two therapeutic groups. The findings of this research are similar to the results of several studies. The study by Eisig et al. [13] indicated that there is no significant difference between STT and sequential therapy. Studies conducted by Yep-Gamarra et al. [14] and Greenberg et al. [15] demonstrated no significant difference between the two methods either. However, some studies have indicated that there is a significant difference in the *H.pylori* eradication rate between these two methods. It could be because of the resistance to Clarithromycin [16,17]. It should be noted that based on the conditions of different countries, Clarithromycin resistance could be different [18,19,20].

Numerous studies have been conducted to compare these two methods in different countries around the world. Some of these studies found that sequential therapy has a higher efficiency in *H.pylori* eradication compared with STT [8,9,10,12,21]. But in some other studies, no difference was observed between the two [13,14,15,22]. Several factors, such as the patient's age and adherence to medicines and treatment, the difference in the prevalence of *H.pylori* with Cag A genotype, gastric acid concentration, and the individual's response to PPI, not only affect the site and antibiotic resistance, but could also have an effect on the eradication of *H.pylori* [19, 23]. However, this study did not investigate the concentration of gastric acid, antibiotic resistance, the minimum inhibitory concentration (MIC), or the genotypes of *H.pylori*. The basic eradication rate in STT has been declining in recent decades [5,6,8]. The primary resistance of *H.pylori* to Clarithromycin is very low [24,25]. The resistance has gradually increased following the extended use of Clarithromycin in recent years. The eradication rate of sequential therapy in this study was lower compared with western countries. The main cause of failure of the eradication of *H.pylori* is antibiotic resistance. The beta-lactamases produced by the resistant strains

of *H.pylori* could be a possible mechanism of inefficiency in amoxicillin-based STT [26]. Antibiotic resistance patterns are different among various geographical areas so that alternative antibiotics may increase the eradication rates based on the local resistance rates. Therefore, it could justify the effects of sequential treatment regimen in different countries [27]. The sequential therapy regimen is a new strategy that was introduced to increase the efficacy and eradication rate and decrease the side effects of the drugs [8,10,11]. In addition, the use of three antibiotics improves the effectiveness of the treatment [28]. In sequential therapy, PPI and amoxicillin are usually used in the first phase of the treatment, and PPI plus Clarithromycin and Imidazol (Tinidazol or Metronidazol) are used in the second phase, which results in the eradication rate of 90% [9,10,11,17]. According to the eradication rates in the second phase, sequential therapy is recommended as the treatment of choice for removing *H.pylori* in Europe [1,5,6].

Abdominal pain was the most common side effects in the STT group, and anorexia in the sequential therapy group. Other symptoms, like nausea, vomiting, diarrhoea, constipation, rashes, and headache, were observed in both groups, from mild to different degrees of severity. Although the observed side effects in the two groups were not statistically significant, in the study by Eisig et al [13], epigastric pain, nausea, diarrhoea, bloating, heartburn, headache, and bitter taste have been reported as the most common adverse events. Several side effects that observed in this study and other studies are consistent with our study finding [13,21,29]. The difference in the side effects reported may be due to the differences in the characteristics of patients in each country [30].

Given that in this study, no difference was observed between these two therapeutic regimen for the eradication of *H.pylori*, it seems that the choice should be applied based on the physician's viewpoint and the patient's condition. The treatment costs also should be considered in addition to these two factors. This study had some limitations, such as the small sample size. The treatment costs of the two methods were not considered either. The lack of estimation of the Clarithromycin resistance level in this study is also a noteworthy limitation. The important reason for the lack of consistent between the results is the imidazole type used in the study.[15,16] Many studies have reported that due to the longer half-life of tinidazole and high rates of resistance to metronidazole, the use of tinidazole in therapeutic regimens may increase treatment success [18,19].

According to the high prevalence of *H.pylori* in Iran [17,25] and increasing resistance to Clarithromycin, further studies are needed to compare the efficacy of these two therapeutic regimen for H.pylori eradication in the country.

5. CONCLUSION

The findings showed that there is no significant difference between two therapeutic regimen of sequential therapy and triple therapy for *H.pylori* eradication. However, further studies with large sample sizes can be useful in choosing the better therapeutic regimen.

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