Comparing the Efficacy of Sequential and Standard Quadruple Therapy for Eradication of *H. Pylori* Infection

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ABSTRACT

Background: The aim of this study was comparison the effectiveness of sequential and standard quadruple therapy on eradication of *H. pylori* infection.

Methods: This clinical trial study was conducted on 160 patients with dyspepsia or gastroduodenal ulcer. Patients were randomly divided into two groups. Group A (standard regimen) received omeprazole, amoxicillin, clarithromycin and bismuth subcitrate for 2 weeks. Group B (sequential regimen) received omeprazole and amoxicillin in 5 days and omeprazole, tinidazole and levofloxacin in 5 days. After the end of treatment regimens, 20 mg omeprazole was administered twice daily for 3 weeks. *H. pylori* eradication was assessed 2 months after antibiotic treatment via fecal antigen.

Results: Frequency of *H. pylori* eradication in group A and B was observed in 55 (68.8%) and 63 patients (78.8%), respectively. No significant difference was seen between two groups, regarding *H. pylori* eradication ($p = 0.15$). The most common side effects in group A, B were bitterness of mouth (63.8%) and nausea (16.2%), respectively ($p < 0.001$).

Conclusion: Although no significant difference was seen between two groups regarding eradication of *H. pylori* infection, higher rate of *H. pylori* eradication was seen in group B than group A. Thus, sequential regimen was a more appropriate regimen with fewer complications.

KEYWORDS

H. pylori infection; Sequential therapy; standard triple-drug therapy; eradication

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is a worldwide and chronic infection. Its incidence is related to several factors including rate of acquisition of infection with *H. pylori*, rate of loss of the infection, and long-term survival of bacteria in the gastric mucosa between infection and eradication (1). *H. pylori* infection is associated with incidence of gastrointestinal diseases such as peptic ulcer, gastric inflammation and gastric cancer (2). *It* may lead to dyspeptic symptoms via changing the gastric acid secretion (3, 4), post-infective alterating gastroduodenal mucosa and activating inflammation of gastric mucosa (4). The prevalence of *H. pylori* infection in developing countries is greater compared to developed countries (3). Furthermore, this prevalence varies in different countries and geographic regions of Asia (5). In this regard, prevalence rate in Japan, China, and Singapore is 39%, 58%, and 31%, respectively. Moreover, report of *H. pylori* infection rate is different in various areas of Iran (6–7).

Eradicating *H. pylori* prevents the recurrence of disease, decreases the risk of gastric cancer and heals peptic ulcers (8). In addition, after treating with antibiotics, other *H. pylori*-associated disorders including chronic atrophic gastritis, intestinal metaplasia and mucosa-associated lymphoid tissue can be regressed (8). However, an important issue in treatment of anti-*H. pylori* is antibiotic resistance (9) which has an effect on treatment efficacy (10).

Several regimens have been assessed for therapy of *H. pylori* infection in clinical trial studies (11–15). Despite many studies in this regard, the optimal therapeutic regimen is still unclear. Recently, common therapies rely on combination of antimicrobial factors such as levofloxacin, metronidazole, amoxicillin and proton pump inhibitors. Clarithromycin based regimens are considered as standard triple treatment. Recently, increasing resistance to standard antibiotic therapy for *H. pylori* infection has been reported (16–23).

Some studies have shown the performance of sequential therapy for eradication of *H. pylori* infection (24–26). In addition, many studies have shown superiority of sequential therapy on standard triple and quadruple therapy (22–27).

Given that prevalence of *H. pylori* infection in Iran is high (9) and few studies have evaluated efficacy of these two treatments as the first line therapy for *H. pylori* infection in our country, the aim of current study was comparison the effectiveness of sequential therapy and standard quadruple therapy on eradication of *H. pylori* infection.

MATERIALS AND METHODS

This clinical trial study was conducted on patients with dyspepsia or gastroduodenal ulcer referred to Shahid Beheshti hospital, Kashan, Iran during 2018. After taking consent from patients, current research was approved by Kashan University of Medical Sciences.

Inclusion and exclusion criteria were as following.

INCLUSION CRITERIA SELECTION

- Patients over 18 years old with dyspepsia or gastroduodenal ulcer
- Confirmation of *H. pylori* infection by fecal antigen or endoscopic pathological findings
- Willingness to participate in the study

EXCLUSION CRITERIA SELECTION

- Previous eradication of *H. pylori*
- Use of any type of antibiotics and PPI during the 4 weeks prior to the study
- Pregnant and lactating women
- Patients with renal failure
- Patients with untreated heart failure
- Patients with history of gastrectomy or complicated peptic ulcer

Then, 160 patients were selected and randomly divided into two groups (n = 80). Group A (standard 14-day treatment regimen) received omeprazole (20 mg b.d), amoxicillin (1 gr b.d), clarithromycin (500 mg b.d) and bismuth subcitrate (240 mg b.d) for 2 weeks. Group B (sequential regimens) received omeprazole (20 mg b.d) and amoxicillin (1 gr b.d) during 5 days and omeprazole (20 mg b.d), tinidazole (500 mg b.d) and levofloxacin (500 mg b.d) during 5 days (10 days). After the end of treatment regimens, 20 mg omeprazole was administered twice daily for 3 weeks.

Helicobacter pylori eradication was assessed at least 2 months after the end of antibiotic treatment or at least 2 weeks after omeprazole discontinuation via fecal antigen. Information including age, sex, history of *H. pylori* infection, history of non-steroidal anti-inflammatory drugs and alcohol intake and smoking were extracted from medical records.

STATISTICAL ANALYSIS

Data were entered SPSS, version 19. Chi square test and Fisher exact test were used for analysis of data. P-value < 0.05 was considered statistically significant.

RESULTS

In current study, 160 patients were classified to two groups. The mean age of patients in group A and B was 45.92 ± 14.18 and 41.43 ± 13.61 (p = 0.043).

Other characteristics of patients in two groups are shown in Table 1.

As shown in Table 1, no significant difference was seen between two groups, in terms of characteristics such as sex, smoking, History of *H. pylori* infection and Taking non-steroidal anti-inflammatory drugs (p > 0.05).

Frequency of *H. pylori* eradication in two groups is shown in Table 2.

As shown in Table 2, no significant difference was seen between two groups, regarding *H. pylori* eradication (p > 0.05).

Frequency distribution of side effects in two groups is demonstrated in Table 3.

Tab. 1 Characteristics of patients in two groups.

Variables	Standard regimen (A)	Sequential regimen (B)	p-value Chi Square test
Sex			
Men	36 (45%)	28 (35%)	0.197
Women	44 (55%)	52 (65%)	
Smoking	11 (13.8%)	6 (7.5%)	0.200
Taking NSAIDs	18 (22.5%)	20 (25%)	0.710
History of *H. pylori* infection	5 (6.2%)	7 (8.8%)	0.548

NSAIDs: Non-steroidal anti-inflammatory drug

Tab. 2 Frequency of *H. pylori* eradication in two groups.

Eradication	Standard regimen N (%)	Sequential regimen N (%)	p-value Chi Square test
Yes	55 (68.8)	63 (78.8)	0.151
No	25 (31.2)	17 (21.2)	

Tab. 3 Frequency distribution of side effects in two groups.

Complications	Standard regimen	Sequential regimen	p-value Fisher exact test
Headache	0 (0)	2 (2.5)	<0.001
Dizziness	0 (0)	3 (3.8)	
Bitterness of mouth	51 (63.8)	10 (12.5)	
Nausea	1 (1.2)	13 (16.2)	
Stomach ache	0 (0)	3 (3.8)	
Diarrhea	0 (0)	2 (2.5)	
Tendonitis	0 (0)	8 (10%)	
joint pain	0 (0)	2 (2.5)	
Skin lesions	0 (0)	1 (1.2)	
No complication	28 (35)	36 (45)	

As shown in Table 3, the most common side effect in group A and B was bitterness of mouth and nausea, respectively ($p < 0.001$). Moreover significant differences was observed between two groups, regarding bitterness of mouth ($p < 0.001$) (Chi square test).

Logistic regression analysis of studied variables is presented in Table 4.

After eliminating confounding effect of independent variables, there was no significant difference between two groups, regarding eradication of *H. pylori* infection (Table 4).

Tab. 4 Logistic regression analysis of studied variables in treatment of *H. pylori* infection.

	B	S. E.	Wald	df	P
Group	0.5210	0.381	1.866	1	0.172
Gender	0.0370	0.421	0.008	1	0.930
Age	-0.0060	0.013	0.189	1	0.664
NSAID taking	-0.0621	0.412	2.271	1	0.132
Smoking	-0.0327	0.627			
History of *H. pylori* infection	-0.0694	0.635	1.193	1	0.275
Constant	1.2870	0.712	3.272	1	0.070

DISCUSSION

H. pylori infection is not associated with symptoms in 50% of cases. However, some individuals develop inflammation of the gastritis or ulcers in the stomach or upper small intestine (28–31). Moreover, *H. pylori* infection causes mortality and morbidity with an economic impact, thus requiring a proper therapeutic approach. Physicians usually treat stomach pain and ulcers created by *H. pylori* via combination of various antibiotics for several days. Recently, increasing resistance to standard antibiotic therapy for *H. pylori* infection was reported (16–22). Actually after standard therapy, infection was observed in one of every six patients with peptic ulcer disease. Therefore, *H. pylori* treatment is a challenge for physicians and no current first-line therapies are capable to treat the infection in all treated individuals (32). Based on findings of recent studies, sequential therapy is identified as first-line therapy in treatment of patients with *H. pylori* infection (32).

The findings of current study showed that the sequential regimen was superior to the quadruple therapy in the treatment of *H. pylori* infection, although no statistically significant were observed between two groups. In this study 78.8% of patients in sequential group and 68.8% of patients in quadruple diet group have recovered. Vaira et al., assessed sequential therapy versus standard triple therapy for eradication of *H. pylori*. The findings showed that eradication with sequential therapy was greater than standard therapy in these patients, which was consistent with our study (32).

Sánchez-Delgado et al., assessed ten-day sequential therapy for *H. pylori* eradication. They selected 139 patients and sequential regime consisted of a 10-day treatment such as a proton pump inhibitor b.d., 1 g b.d. amoxicillin for the first 5 days, followed by a PPI b.d., 500 mg b.d. clarithromycin and 500 mg b.d. metronidazole for the next 5 days. According to findings of this study, eradication was seen in 117 out of 129 patients who returned. It seems that sequential treatment is effective for eradicating *H. pylori* (33). Zhou et al., in China assessed sequential therapy regimen compared to conventional triple therapy for *H. pylori* eradication. Then, patients in group A received clarithromycin (500 mg), esomeprazole (20 mg) for the first 5 days, following esomeprazole (20 mg), clarithromycin (500 mg), amoxicillin (1000 mg) for the remaining 5 days. Group B received esomeprazole (20 mg), amoxicillin (1000 mg) for 5 days, followed by clarithromycin (500 mg), esomeprazole (20 mg), and amoxicillin (1000 mg) the remaining 5 days. The findings of this study showed that both treatments can alleviate symptoms in patients. Moreover, they believed that sequential therapy was better than standard

triple therapy (24). Marshall et al., compared efficacy of sequential therapy with standard triple therapies during 7–10 days. The findings showed that the success of sequential regimen was higher than standard triple therapies during 7–10 days (34). Gatta et al., reported eradication rate following triple therapy and sequential therapy were 35.1% and 83.9%, respectively (35).

Varia et al., reported 7–14 days triple therapy is reducing around the world with unsatisfactory low eradication rate in various country. They believed that sequential therapy is the most effective in first-line therapy and had superiority over standard triple therapy on more than 2300 treated patients. In addition, they reported that the sequential therapy is successful against those clarithromycin-resistant strains that have the A2143G point mutation, which significantly reduces the effectiveness of standard triple therapy (32). The precise mechanism of sequential therapy was unknown. There are several reasons, but all remain unconfirmed at this time.

One of the reasons is that reducing the bacterial density in the stomach via medications including amoxicillin and improving the efficacy of subsequently administered combination such as tinidazole and clarithromycin (36).

In addition, the most common side effects in group A and B was bitterness of mouth and nausea, respectively. Moreover, significant difference was observed between two groups, regarding side effects. Kaboli et al., compared sequential regimen and standard therapy for *H. pylori* eradication. The findings showed significant difference between two groups, regarding side effects, which was consistent with our study (37). Aminian et al., compared sequential regimen and standard quadruple therapy in patients with dyspepsia. The findings showed that there was significant difference between sequential regimen and standard quadruple regimen, considering side effects (38). This study also was consistent with our study.

It is noteworthy that the eradication rate of Helicobacter pylori in the two treatment groups was compared with controlling confounding variables of age, sex, use of nonsteroidal anti-inflammatory drugs, smoking and family history of Helicobacter pylori infection via logistic regression analysis (Table 4). This caused to control the effect of confounding factors.

CONCLUSION

Although no significant difference was seen between two groups in terms of eradication of *H. pylori* infection, higher rate of eradication of *H. pylori* infection was observed in sequential treatment regimens than standard regimens. Therefore, it was considered as a more appropriate treatment regimen compared to standard regimens in first-line therapy of *H. pylori* infection. In addition, this medication regimen was associated with fewer side effects.

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