

## Efficacy of standard triple therapy versus bismuth-based quadruple therapy for eradication of *Helicobacter Pylori* infection

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### ABSTRACT

*Helicobacter Pylori* is the main cause of gastric ulcer, adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. Up to now, different regimens have been used for *Helicobacter pylori* (*H.pylori*) eradication to find the most potent and cost-effective regimen with less side effects. The aim of this study was to investigate the efficacy of standard triple therapy versus quadruple therapy for eradication of *H. pylori*. In a randomized clinical trial, 110 patients with *H.pylori* infection were randomly assigned into two groups of triple or quadruple therapy. The first group received standard triple therapy regimen with clarithromycin, amoxicillin and omeprazole and the second group received bismuth-based quadruple therapy regimen. At the end of study, stool antigen assay was used to confirm *H.pylori* eradication. The mean age of patients was  $41.58 \pm 11.98$  years and 50.9% of them were male. Side effects of treatment with triple therapy were observed in 49.1% of cases. *H.pylori* eradication rate with triple and quadruple therapy regimen was 54.5% and 72.7% respectively but the difference was not statistically significant. Results showed that the efficacy of triple therapy was comparable to that of bismuth-based quadruple therapy regimen. However, due to the better compliance of triple therapy regimen, it is recommended for the first line treatment. Quadruple therapy could be used as an alternative treatment when triple therapy fails.

**Keywords:** *H.pylori*; Eradication; triple Therapy Regimen; Quadruple Therapy Regimen.

### INTRODUCTION

The rate of *Helicobacter pylori* (*H. pylori*) colonization in the stomach in the United States and developed countries is about 20% and in most of developing countries is more than 80% in the adult population. The prevalence of *H.pylori* infection in the USA is age related. About 50% of individuals around 60 years old are infected, and 25% of people in the age of 30 are *H.pylori* positive [1, 2]. Very low incidence of *H.pylori* among children in developed countries is due to the high life standards and increased use of antibiotics [1, 2]. *H. pylori* is the main inducer of chronic gastritis, gastric and duodenal ulcers, mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer; so the treatment of *H. pylori* infection is very important. In the past 20 years, the standard triple-drug regimen (PPI amoxicillin, clarithromycin, metronidazole) has been used widely in many countries as the first line treatment (Maastricht I, II)[3]. However, the

standard triple-therapy regimen has certain limitations, just like other available antibiotics. Because of the side effects, patient compliance is reduced and drug resistance has increased [4, 5]. In recent years, a progressive decrease has been observed in the eradication rate of *H. pylori* because of resistant to clarithromycin and metronidazole [6, 7]. The efficacy of double, triple and quadruple regimens have been shown in 73 clinical trials that revealed an *H.pylori* eradication rate of 61 to 93%. The reason for this low rate of eradication is not clear, but it seems that it is related to antibiotic resistances [8]. Sasaki et al. evaluated the *H.pylori* resistance and eradication rate from 1995 to 2008. They determined the increasing rate of resistance from 8.7% to 54.5% and reducing rate of eradication from 90.6% to 74.8% [9]. Now, considering the relationship between *H.pylori* infection and gastric cancer, using drug regimens that are effective in reducing the

prevalence of *H.pylori* infection is necessary [9]. Up to now, different regimens have been used *H.pylori* eradication to find the most potent and cost-effective regimen with less side effects.

This study aim was to investigate the efficacy of standard triple therapy regimen versus quadruple-drug therapy for eradication of *H. pylori* infection in Iranian patients.

## MATERIALS AND METHODS

This randomized clinical trial was conducted in Modarres Hospital, Tehran, Iran during 2011-2012. The study was conducted according to the principles of Helsinki deceleration and ethics committee at Shahid Behehsti University of Medical Sciences approved the study protocol. All patients signed written informed consent form before enrollment.

Patients with dyspepsia, aged between 18 and 60 years with positive UBT or serology test, and patients with dyspepsia older than 45 years who underwent endoscopy were included in the study. Patients with acute complications of peptic ulcer disease such as bleeding, obstruction, those aged more than 60 or less than 18, those took the same antibiotic during the last four weeks and those with allergic reaction to drugs and non-compliance with drug regimen were excluded from the study.

Patients with dyspepsia were selected randomly among the patients who referred to the gastroenterology clinic of Modarres hospital. They were examined for *H. pylori* infection with serology test or endoscopy (if necessary) or Urea Breath Test (UBT) or biopsy.

The patients with positive *H.pylori* infection were divided randomly into two groups of 55 individuals. Then the patients were treated

separately with triple or quadruple drugs regimens for 14 days. Four weeks after completion of therapy, the eradication of *H. pylori* was evaluated by fecal antigen test. Stool-based test (SAA) was performed by ELISA II method.

One group received standard triple therapy regimen with omeprazole (20mg b.i.d), amoxicillin (1 gr b.i.d) and clarithromycin (500 mg b.i.d) for 14 days. The other group received bismuth-based quadruple therapy regimen with omeprazole (20mg b.i.d), bismuth (one tablet b.i.d), metronidazole (250mg q.i.d) and tetracycline (500mg q.i.d) for 14 days.

Previous studies have shown that *H.pylori* eradication by triple therapy (clarithromycin, amoxicillin, omeprazole) is about 60% (4) and about 25% by quadruple regimens (bismuth, tetracycline, metronidazole, omeprazole).

### Statistical Analysis

Statistical analyses were done using SPSS software ver.17.00 for Windows. To describe the data, mean, standard deviation, frequency and percentage were reported. For comparison of categorical data between the two groups, chi-square and Fisher's exact tests were used. Independent sample t-test was used to compare numerical data with normal distribution between the two groups. P value less than 0.05 was considered significant.

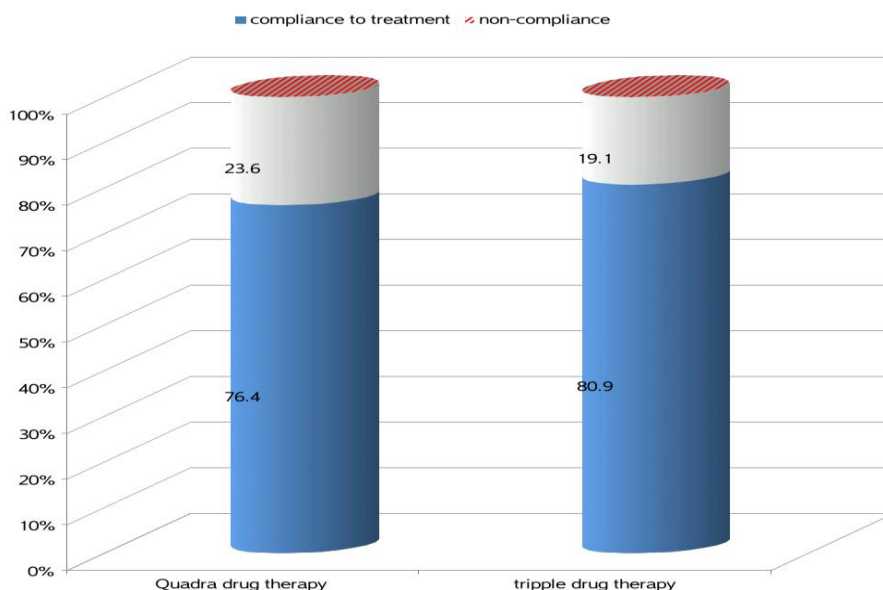
## RESULTS

In this study, at first 146 patients were included in the study but 34 patients (23.6%) lost-to- follow-up in the next study steps, which 21 (27.6%) of them were in quadruple therapy regimen and 13 (19.1%) were in triple therapy regimen ( $p>0.05$ ) (Figure 1).

**Table 1:** Demographic and clinical information of two study groups

Variable	Triple therapy group	Quadruple therapy group	All patients	P value
n	55	55	110	
Gender, n	30F, 25 M	24 F, 31M	54F, 56M	NS
Age, year, (mean $\pm$ SD)	41.38 $\pm$ 11.41	41.78 $\pm$ 12.6	41.58 $\pm$ 11.98	NS
<b>Methods of H.pylori diagnosis</b>				
Urea Breath Test, n(%)	47 (85.5)	50 (90.9)	97 (88.2)	NS
Serologic Test, n(%)	5 (9.1)	2 (3.6)	7 (6.4)	NS
Biopsy and Histology, n(%)	3 (5.5)	3 (5.5)	6 (5.5)	NS

NS: non significant



**Figure 1.** number of drop out in each study group

Finally, 110 patients in two groups of 55 individuals completed the study and performed follow-up test with fecal Antigen test. The mean age of patients was  $41.58 \pm 11.98$  years (ranged 18-60) and 49.1%

of patients were female. Demographic information of two study groups has been shown in Table 1. There was no significant difference between the two groups regarding age and gender ( $p > 0.05$ ).

**Table 2.** Endoscopic finding in two study groups

Finding	Triple therapy group	Quadruple therapy group	All patients	P value
Normal, n(%)	24 (43.6)	23 (41.8)	47 (42.7)	NS
Erosive gastritis, n(%)	16 (29.1)	18 (32.7)	34 (30.9)	NS
Gastric ulcer, n(%)	6 (10.9)	4 (7.3)	10 (9.1)	NS
Duodenal ulcer, n(%)	9 (16.4)	10 (18.2)	19 (17.3)	NS

NS: non significant

**Table 3.** Treatment side effects in two study groups

Side Effect	Triple therapy group	Quadruple therapy group	All patients	P value
Abdominal distention, n(%)	12 (21.8)	6 (10.9)	18 (16.4)	NS
Abdominal pain, n(%)	4 (7.3)	12 (21.8)	16 (14.5)	NS
Constipation, n(%)	6 (10.9)	8 (14.5)	14 (12.7)	NS
Nausea and vomiting, n(%)	4 (7.3)	7 (12.7)	11 (10.0)	NS
Decreased appetite, n(%)	5 (9.1)	4 (7.3)	9 (8.2)	NS
Impaired sense of taste, n(%)	4 (7.3)	5 (9.1)	9 (8.2)	NS
Coetaneous rash, n(%)	5 (9.1)	2 (3.6)	7 (6.4)	NS
Diarrhea, n(%)	5 (9.1)	1 (1.8)	6 (5.5)	NS
Total, n(%)	27 (49.1)	25 (45.5)	52 (47.3)	NS

NS: non significant

*H.pylori* infection was detected by different methods in our patients. Methods of *H.pylori* infection diagnosis in both study groups has been shown in Table 1. There was no significant difference between the two groups regarding the method of

*H.pylori* infection diagnosis ( $p > 0.05$ ). Results of endoscopic examination in two study groups have been demonstrated in Table 2. There was no significant difference between the two groups regarding endoscopic findings ( $p > 0.05$ ). Overall,

complete *H.pylori* eradication was found in 70 patients (63.6%) based on stool-based test (SAA). Although, *H.pylori* eradication rate in quadruple therapy group was higher than the triple therapy group but this difference was not statistically significant (72.7% vs. 54.5%) ( $p$ : 0.27). The compliance with the treatment in quadruple therapy group (27.6%) was numerically more than triple therapy group (19.1%) but the difference was not statistically significant ( $p > 0.05$ ). Side effects of two treatment regimens have been reported in Table 3. No significant difference was found between the two groups regarding the treatment side effects ( $p$ : 0.811).

## DISCUSSION

This study showed equal efficacy of standard triple and quadruple therapy regimens in *H.pylori* eradication. *H. pylori* is a gram-negative bacterium that has been colonized normally in human's body. Human is the only reservoir of *H. pylori*. Children either receive these bacteria from their parents (usually their mother) or other children. The fecal-oral or oral-oral transmission is not clearly specified [1]. It is estimated that about half of the human population are infected with *H. pylori*. Perhaps *H.pylori* is the most prevalent infection that can cause several complications in human [10]. In an Iranian study, the prevalence of *H. pylori* infection in patients over 10 years old has been reported 36.5% [11]. Patients' compliance with triple therapy and quadruple therapy has been reported between 70% and 97%, respectively [12-15]. In our study, the compliance with treatment in triple and quadruple treatment groups was not significantly different. This was in line with the findings of previous studies [13]. The reason could be due to the side effects of drugs in quadruple regimen instead of triple therapy.

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The most prevalent complications of treatment in this study were abdominal bloating, abdominal pain and constipation. Moghaddam and colleagues reported similar results but abdominal pain was the most observable complaint in patients using quadruple therapy which was seen in quadruple therapy more than triple therapy group. In this study, the efficacy of two regimens was similar. Eradication rate of *H.pylori* by triple therapy regimen has been reported from 50% to 90.7% [9,13,16-19] while the eradication rate by quadruple therapy regimen has been reported 35.9%-84.1% [12-14,19, 20]. There are no significant differences in the majority of published studies between the eradication rate of triple and quadruple regimens [12-15].

There was only one study that had found a significantly higher eradication rate of triple therapy with omeprazole, clarithromycin and amoxicillin that compared to quadruple therapy with omeprazole, amoxicillin, metronidazole and bismuth (90.7% vs. 84.1%,  $p = 0.0001$ ) [19].

## CONCLUSION

According to our findings, there is no significant difference between the triple therapy and quadruple therapy regimens in terms of eradication rate of *H. pylori* and the side effects (except for abdominal pain). Due to better patients' compliance, triple therapy is recommended as the first-line treatment for *H.pylori* eradication. Quadruple drug therapy could be useful in cases with resistance or treatment failure.

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