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COMPARISON OF 7 - DAY CONCOMITANT THERAPY REGIMEN VERSUS CLASSIC TRIPLE THERAPY REGIMEN IN *HELICOBACTER PYLORI* ERADICATION: A RANDOMIZED CLINICAL TRIAL

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ABSTRACT: There are various treatment regimens including different antibiotics and antacid medications for eradicating *Helicobacter pylori* to compare the effectiveness of 7-day concomitant regime with classic triple regimen in eradicating *H. pylori*. In this randomized clinical trial, 206 dyspeptic patients proven *H. pylori* infection, attended to a gastrointestinal clinic in Khorramabad (west of Iran) were studied. The patients were randomly divided in two equal groups. Classic group were treated for 14 days with a regimen including omeprazole 20mg, amoxicillin 1g and clarithromycin 500mg, twice daily. In concomitant group, the patients were treated for 7 days with a regimen including omeprazole 20mg, amoxicillin 1g, clarithromycin 500mg and metronidazole 500mg twice daily. During the treatment period and a week after the end of treatment, the patients were evaluated in terms of possible side-effects and medication acceptance and tolerance. For confirmation of eradication, 6 weeks after the end of treatment, urea breath test with carbon 13 (UBT) was done for both the groups. Data were analyzed using descriptive statistics, T-test and chi-square test, logistic regression through SPSS software version 21. The level of significance was considered less than 0.05. *H. pylori* eradication rate in classic group was 68.9% and in concomitant group was 83.4%. (p - value = 0.03). The incidence of gastrointestinal side-effects was not statistically different between the groups. *H. pylori* eradication rate in 7-day concomitant treatment regimen is more than 14-day classic regimens. Therefore, it is suggested to use 7-day concomitant regimen as first-line of *H. pylori* eradication.

INTRODUCTION: A large proportion of the world's population has been infected by *Helicobacter pylori* (*H. pylori*).

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The most important cause of gastric and duodenal ulcer disease is infection with *Helicobacter pylori* [1]. *H. pylori* are a gram negative, curved rod-shaped, flagellated bacterium that was introduced in 1982. This bacterium residents in the gastric mucosa and afflicts nearly 50% of the world population and results in problems such as dyspepsia, peptic ulcer disease, gastric cancer, gastric MALToma. *Helicobacter pylori* are more common in developing countries [2].

The prevalence of *Helicobacter pylori* in Iran is 30.6% to 82% [3]. *H. pylori* eradication is recommended in the patients with proven peptic ulcer disease [4]; Peptic ulcer disease is not be considered as the only indication of *H. pylori* eradication, family history of gastric cancer, MALToma and early gastric cancer are among other indications for *H. Pylori* eradication [5, 6]. *H. pylori* eradication can have preventive effect on peptic ulcer disease, recurrent bleeding, gastric adeno carcinoma and gastric MALToma and result in reducing recurrence of *H. pylori* infection and enhancing peptic ulcer healing [7, 8].

Indiscriminate and often unnecessary use of antibiotics increases resistance to antibiotics such as antibiotics affecting *H. pylori*. Resistance to clarithromycin has increased from 5 percent to nearly 20 percent over the past 10 years [6]. Appropriate and acceptable regimen for the eradication of *H. pylori* is the regimen by which the eradication rate is over 85 percent [5]. A 14-day classic triple therapy regimen (containing a proton pump inhibitor, clarithromycin with metronidazole or amoxicillin) has been approved as first-line treatment in many countries, including Iran. This regimen is named Standard Triple Therapy (STT). The effectiveness of this treatment regimen has decreased in the past decade [6, 9] and in recent studies in some countries, the *H. pylori* eradication rate by this regimen has reached to an unacceptable level (≤ 80 percent) [10, 11].

The researchers believe that one of the main reasons for the increase in *H. pylori* eradication rate is resistance to antibiotics such as clarithromycin and metronidazole [6]. This issue has led to conduct vast research on alternative first-line therapeutic regimens and the investigation on Sequential, concomitant and hybrid therapy regimens has been suggested. Concomitant regimen has been defined as quadruple therapy containing proton pump inhibitor with three antibiotics with or without bismuth that has been studied in various time intervals of 3 days to 14 days [12, 13]. Considering the rising resistance to some antibiotics and declining the efficacy of common therapeutic regimens, this study aimed to compare the effectiveness between the classic triple therapy regimen and seven day concomitant therapy regimen to achieve therapeutic regimens with optimal therapeutic efficacy.

MATERIALS AND METHODS: This study was a randomized clinical trial conducted on dyspeptic patients attended to Shohada-ye-Ashayer Hospital of Khorramabad (a city in west of Iran) from October 2015 to March 2015 (IRCT20160126237 36N2). In this study, cases with proven *H. pylori* infection that had indications of *H. pylori* eradication were studied in term of efficacy of therapeutic regimens. Indications for *H. pylori* eradication included an *H. pylori* positive gastric biopsy and the co-existence of duodenal ulcer, gastric ulcer, gastric malt lymphoma, early gastric cancer and family history of gastric cancer.

Inclusion Criteria: A proven *Helicobacter pylori* infection based on indication for *H. pylori* eradication and consent for participation in the study. After obtaining written consent, participants were enrolled into the study. Exclusion criteria: age less than 18 years, history of allergies to medications, history of previous *H. pylori* eradication, recent history of antibiotic use (in the last month), pregnancy, presence of cirrhosis and chronic renal failure.

A convenience sample of dyspeptic patients attended to the GI clinic of Shohada-ye -ashayer hospital, were selected and assigned into in the study groups randomly. 214 patients who met the inclusion criteria of the study were randomly divided into two equal groups of 107 patients: the classic 14-day regimen and the 7-day concomitant regimen. The patients of classic regimen group received Omeprazole 20 mg; amoxicillin 1 g and clarithromycin 500 mg twice a day for 14 days and the patients of concomitant regimen group were treated with omeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg and metronidazole 500 mg twice a day for 7 days.

During the first week of treatment, the patients were visited in term of side effects and drug tolerance, and all data were recorded. Then, they were re-called one week after the end of treatment. 6 weeks after completion of treatment, urea breath test with Carbon 13 was performed in the both groups to confirm the eradication of *Helicobacter pylori* and if this test was negative, *H. pylori* eradication would be reported. Data were analyzed using Chi-square test and logistic regression through SPSS statistical software (version 21).

RESULTS: In this study, 214 patients with *Helicobacter pylori* infection were randomized to two groups of 107 patients for receiving classic therapy or concomitant therapy from the 7-day concomitant regimen group, 2 patients were excluded because of drug adverse effects and another 2 cases did not attend for eradication testing. From the classic regimen group, 3 cases for serious side effects of drug and 1 case for lack of cooperation were excluded. Ultimately, 103 samples completed the study in each group (**Fig. 1**). The average age of the samples, in the classic regime group and concomitant regime groups were 42 ± 11.88 years and 41 ± 13.75 years respectively. Patients were classified in the age groups of under 30 years, 31 - 40 years, 41 - 50 years and over 50 years. Most of the patients in both groups 31.1% (64 cases) were in the age group of 31 - 40 years, In the concomitant group, 46.6% (48 patients) were male and 53.4% (55 cases) were female, and in the Classic group, 49.5% (n = 51) were male and 50.5% (n = 52) were female. The demographic data for each therapeutic group are summarized in **Table 1**. Statistical analysis showed no significant difference between concomitant and classic treatment groups in terms of age and sex of patients.

TABLE 1: THE DEMOGRAPHIC DATA OF PATIENTS BASED ON THE THERAPY GROUP

		Concomitant No (%)	Standard No (%)
Gender	Male	48(46.6%)	51(49.5%)
	Female	55(53.4%)	52(50.5%)
Age (years)	(mean ± SD)	41 ± 13.75	42 ± 11.88
	≤ 30	18(17.5)	18(17.5)
	31 - 40	32(31.1)	32(31.1)
	41 - 50	22(21.3)	25(24.2)
	≥ 50	31(30.1)	28(27.2)
Education	Illiterate - elementary	32(31.1)	34(33)
	High school	14(13.6)	9(8.7)
	diploma	41(39.8)	49(47.6)
	College	16(15.5)	11(10.7)
Smoking	Cigarette	9(8.7)	7(6.8)
	Hookah	6(5.8)	4(3.9)
	Cigarette and Hookah	4(3.8)	7(6.7)

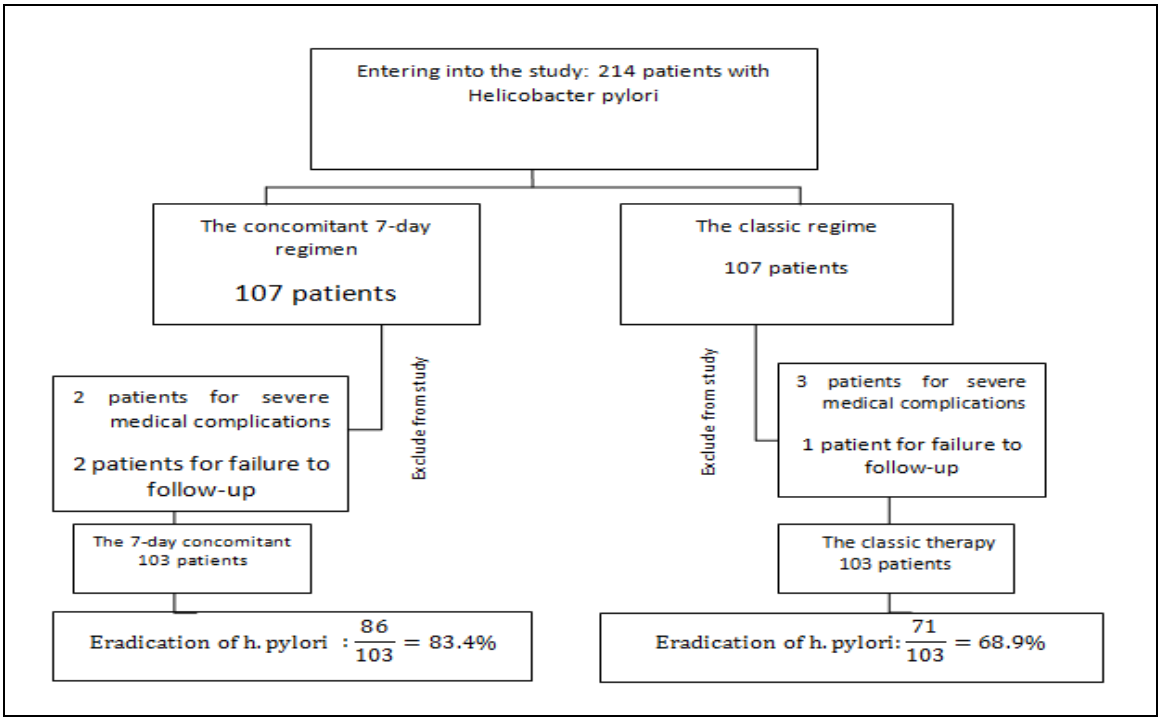

FIG. 1: THE COMPARISON OF THE CLASSICTRIPLE REGIMEN AND THE 7-DAYS CONCOMITANT REGIMEN IN THE *HELICOBACTER PYLORI* ERADICATION

The eradication rate of different age groups, showed no statistically significant difference between two groups. The highest Eradication rate was in the under 30 years age group, Although the eradication of *Helicobacter pylori* in the patients under 30 years of age was significantly higher than in the patients over 30 years of age, statistical analysis using logistic regression model showed no significant difference. Also no significant relation-ship was observed between *H. pylori* eradication and gender, education level and smoking among the intervention groups. The side effects were reported in 17 patients (16.6%) in the classic regimen group and in 15 patients (14.6%) in the Concomitant regimen group but the differences were not statistically significant.

The most common side effects were abdominal pain in 12 patients and nausea and headache in 12 patients in the classic regimen group and abdominal pain and nausea in 5 patients in the Concomitant regimen group. Using logistic regression model, no significant differences were observed between two groups in terms of side effects. The success of *H. pylori* eradication in the classic triple regimen group was 68.9% and in the concomitant regimen was 83.4%. Therefore, the eradication rate in the concomitant regimen was higher than in the classic regimen and this difference was statistically significant (p-value = 0.03).

DISCUSSION: The ideal and acceptable therapeutic regimen for *H. pylori* infection treatment should be simple, short-term, well-tolerated and high eradication rate. Short-term duration therapeutic regimens have many benefits including lower cost, higher compliance, as well as lower side effects and drug resistance [12, 13].

In our study, the eradication rate in the Concomitant therapy group was higher than in the classic therapy group. In other words, the effectiveness of the 7-day concomitant therapy is higher than that of the classic regimen. An acceptable *H. pylori* eradication rate in the standard regimen should be at least 85%. Although the eradication rate in the 7-day concomitant regimen is higher than in the 14-day classic regimen, this rate in the two groups is lower than the standard rate. This may be attributed to drug resistance depending on the geographic region. More researches in this area are necessary. Kwon *et al.*, in South Korea in 2011 studied the effect of concomitant 7-day treatment regimen (Lansoprazol (30mg / bid), amoxicillin (1g / bid), clarithromycin (500mg / bid) and metronidazole (500mg /bid) on the *Helicobacter pylori* eradication. The eradication rate in their study was 89.8% [14] that is relatively consistent with the present study.

A study by Moghaddam M *et al.,* aimed to comparing the triple therapy vs quadruple therapy (concomitant) for the eradication of *Helicobacter pylori* in 56 patients with chronic dyspepsia. In this study, the treatment success rates based on UBT in the triple therapy and quadruple therapy were 50% and 48% respectively and not significant difference observed between the two therapeutic methods. Results of that study are inconsistent with the findings of our study. The eradication rate in both concomitant therapy and classic regimen were lower than our study. This difference may be explained by differences in the demographic characteristics, the severity of disease in the studied populations or differences in resistance to amoxicillin and clarithromycin. However, Small sample size with a high rate of exclusion could have distorted the results of study [15].

In a study conducted by Fattahi *et al*., the eradication rate of triple therapy with omeprazole, amoxicillin and clarithromycin was reported to be 85% and the treatment success in this study was more than in our study. It can be interpreted that in the past decade, the classic (triple) regimen has been effective enough but with increasing in resistance to antibiotics, their effectiveness had been declined.

In our study, the patients were placed in the therapeutic groups by the random block. Most patients were in the age group of 31 - 40 years. The comparison of eradication rates between the different age groups showed no statistically significant difference. Although the *H. pylori* eradication rate in the patients under 30 years of age was more than in the patients over 30 years of age but this difference was not significant, and no significant relationship was observed between the *H. pylori* eradication rate and the patients' age. Also, in Moradi's study (2009), the success of

treatment in the younger patients was more than others and this difference was statistically significant [15].

In the studies of Khalilian *et al.,* [17] and Naghara *et al.,* [18] no significant relationship between the age groups and the treatment success of *H. pylori* was observed. In the present study, there was not significant relationship between the *H. pylori* eradication rate and gender in any of the therapeutic groups. The result of current research is similar to the results of Khalilian *et al*., [17] and Chan *et al.,* Studies [19]. In the present study, education level and smoking were also examined and no relationships were observed between education level, smoking and the *H. pylori* eradication rate. In Similar studies have not also been reported, relationship between education level, smoking and eradication rate.

Due to the use of multi-drug regimens to *Helicobacter pylori* eradication, the incidence of adverse events was expected to be high in the patients treated with these therapeutic regimens. Adverse events were examined in the participants based on the patient's self-report during and after the treatment. Side effects included nausea, vomiting, and abdominal pain, diarrheic, unpleasant taste in the mouth, anorexia, headache, and skin rashes. Side effects were reported by 17 patients (16.5%) in the classic group and by 15 patients (14.5%) in the concomitant group. No significant relationship was found between the rate of side effects and the *H. pylori* eradication rate among the therapeutic groups.

Abdominal pain was the most common side effects; that this finding is not consistent with many studies. In the study of Kwon *et al.,* In South Korea in 2011, an unpleasant taste in the mouth was reported as the most common complication among the samples. The main reason for a metallic taste in the mouth can be attributed to the use of metronidazole [14]. Furthermore Aminian *et al.,* in Iran, reported nausea as the most common side effects [20]. In the study of Chan *et al.,* in China in 2001, the most common complications were nausea, vomiting, dizziness and bad taste in the mouth [19]. Side effects in our study are somewhat close to that of the study by Moradi [15]. However, in our study, fewer side effects (15.5%) were reported that could be due to short time of treatment (in the concomitant group). The review of the literature showed that side effects and their incidence rates are very different in various studies. This could be attributed to racial differences, quality of medicines and differences in the selected groups. However, other studies have also showed no significant correlation between the incidence of adverse side effects and the *H. pylori* eradication rate [14, 19, 21].

CONCLUSION: The 7 - day concomitant regimen is more effective in the eradication of *H. pylori* compared to the 14-day Classic triple regimen. Considering higher effectiveness, shorter treatment period and no difference in the side effects, the 7-day concomitant regimen is suggested to be used as the first-line treatment of *helicobacter pylori*.

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