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Research Article

Randomized Clinical Trial: triple therapy versus 5-day concomitant therapy

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ABSTRACT

Introduction :various therapeutic regimens have been introduced to eradication of helicobacter pylori infection. concomitant regime consists of a proton pump inhibitor (PPI) with three antibiotics. this study was conducted to compare the effectiveness of triple therapy and 5 days concomitant regime.

Method :In this study 193 h. pylori positive patients older than 18 years without previous history of eradicating the helicobacter pylori were studied. The first group (classic) received triple therapy regimens(14 days with omeprazole, amoxicillin and Clarithromycin). The second group (Con-5) was treated with 5-days concomitant regime(omeprazole, amoxicillin, and metronidazole, and Clarithromycin for 5 days). 6 weeks after the completion of treatment Urea Breath Test(UBT) was performed for confirmation of h.pylori eradication.

The eradication rate in the classic group was 68.4% byPP analysis, and 65% by ITT analysis.eradication rate of Con-5 Group were 64.3% and 63% by PP and ITT analysis resptively. No significant difference was observed between two groups in terms of the h. pylori eradication.

Conclusion : No difference between the effectiveness of triple therapy and 5- days concomitant regimes was observed . The effectiveness of both regimes was lower than expected. Further studies with large numbers of samples are needed

Keywords: helicobacter pylori, eradiation,triple therapy, concomitant therapy,dyspepsia

INTRODUCTION :

Several studies have been conducted to access a desired, ideal and safe therapeutic regimen for the eradication of H. pylori infection [1, 2] and various therapeutic regimens with different efficacies have been introduced to eradication of helicobacter pylori infection [3]. Recent studies show that the eradication rate of triple therapy has reached an unacceptable level (less than 80%) [2,3,4]. Decline the effectiveness of triple therapy has caused the introduction of new therapeutic regimens with high efficacy and high tolerability and compliance [1, 2]. The concomitant regime consists of a proton pump inhibitor (PPI) with three antibiotics.[6]

Different studies confirmed the effectiveness of concomitant regime in eradication of H. pylori in 3 to 14 days periods [2, 3,5,6]. The most commonly used antibiotics, especially in the first concomitant regime, were amoxicillin, clarithromycin and metronidazole (or tinidazole) [1, 5, 6]. However, in subsequent studies, other antibiotics like levofloxacin and furazolidone were used in this therapeutic regimen [2, 3, 6]. Various studies suggested that concomitant regime has high efficacy and is more effective than triple therapy [3, 7, 8 , 9]. In a study conducted by Naghara and colleagues in japan , the eradication rate of 5 days concomitant therapy was reported as 98.1% [10]. On the other hand, in a clinical trial by Kongchayanun et al in thailand, the eradication rate of 5 days concomitant regime was 90% [11]. So, based on differences in the effectiveness of different therapeutic regimens in different regions, this study was conducted to compare and investigate the effectiveness of triple therapy regime and 5 days concomitant regime.

MATHERIAL AND METHOD

This study is a randomized clinical trial that was conducted from October 2015 to March 2015. All dyspeptic patients who referred to Shohadaye- Ashayer Hospital of Khorramabad (West of Iran) [Fig 1] were enrolled to study.

In this study all h. pylori positive patients older than 18 years without previous history of eradicating the helicobacter pylori were studied. Exclusion criteria include previous H. pylori eradication history, recent frequent intake of non-steroidal anti-inflammatory drugs, severe underlying disease such as chronic renal failure, cirrhosis, a history of gastric surgery or the presence of gastric cancer, history of allergy to penicillin and other antibiotics and also pregnant and lactating women were excluded. The study is registered in the IRCT: registration number is (IRCT2015082323736N2). Written consent was obtained from all patients for participating in the study .

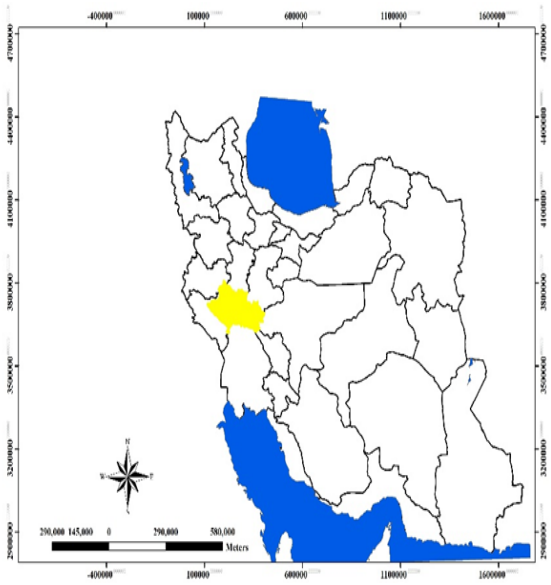

Figure 1. Location of Lorestan province within Iran

Diagnosis of H. Pylori infection

All patients underwent upper gastrointestinal endoscopy before enrolment in this studyv.Helicobacter pylori infection was defined as positive if the results of histological assessment by giemsa stain was positive.

Treatment and Eradication

The eligible patients were randomly assigned to one of two treatment groups. The first group received (classic) triple therapy regimens. Patients were treated for 14 days with omeprazole, amoxicillin and Clarithromycin. The second group (Con-5) was treated with 5-days concomitant regime. The patients received omeprazole, amoxicillin, and metronidazole, and Clarithromycin for 5 days.

All patients were visited two times during the study , once during the treatment and once after completion of the treatment. The patients were questioned on the drug and tolerability of side effects. Adherence is defined based on the number of the consumed pills and administrated drugs. If the patient has consumed more than 90% of the pills, it is considered acceptable. The definition and the basis of the side effects of drugs were based on the patient testimony of complications after starting the medication.

All patients were asked to refer 6 weeks after the completion of treatment for Urea Breath Test. UBT was performed for proving Helicobacter Pylori Eradication using PY test, Kimberly-Clark, USA.

Statistical analysis

The results of this study were analyzed in an intention to treat (ITT) and a per protocol (PP) . ITT analysis included all patients who had taken at least one dose of the medications. The PP analysis was limited to patients who took >90% of the medications . SPSS soft¬ware for Windows (version 19.1; SPSS Inc., Chicago, IL, USA), was used for the statistical analyzes. We compared the eradication rate of two groups using chi-square test, Student's t-test. For all analyses, P values <0.05 were considered significant.

RESULT

Characteristics of Study Groups:In this clinical trial, 200 patients were eligible for the study. 4 subjects did not return to visit and perform UBT test and 3 subjects left the study due to severe drug side effects. At the end, 193 patients completed the study. In the classic group 95 patients were studied which included 46 men and 49 women. Con-5 group included 98 patients (47 men and 51 women). The average ages of Classic group and Con-5 group were 41.1±12.2 years and 41.4±11.4 years respectively.(Table 1)

Variables	classic Group (n=95) N (%)	5days Concomitant Group (n=98) N (%)
Sex		
Male	**46(48.4%)**	47(48%)
Female	**49(51.6%)**	51(52%)
Age (Mean±SD)	**41.4±12.29**	41.49±11.41
18-30	**)18.9%(18**	)20.4%(20
31-40	**)33.7%(32**	)29.6 %(29
41-50	**)29.5%(28**	)23.5%(23
≥51	**)17.9%(17**	)26.5%(26
smoking		
yes	**16(16.8%)**	17(17.4%)
no	**79(83.2%)**	81(82.6%)
education		
illiterate	**)11.6%(11**	14(14.3%)
Primary	**)29.5%(28**	)20.4%(20
Secondary school	**)33.7%(32**	)29.6 %(29
diplomas	**)18.9%(18**	)23.5%(23
Collegue education	**6(6.3%)**	12(12.2%)

Table 1: Baseline demographic and clinical characteristics of patients

Eradication Rate of helicobacter pylori

The eradication rate in the classic group was obtained 68.4% using per protocol analysis, and 65% using the analysis of intention to treat. And against the eradication rate of Con-5 Group was obtained 64.3% using per protocol analysis 3 and 63% using the analysis of intention to treat. The eradication rate of H. pylori in the classic group was more than Con-5 group, and the probability of eradication in classic group was 2.1 times the Con-5 group (OR=1.2). But this difference is not statistically significant (P- value=0.545). No significant difference was observed between two groups in terms of the H. Pilory eradication.(Table 2)

Table 2.eradication rate of triple therapy and concomitant therapy

	not eradicated	eradicated	OR	CI	p-value
Group (classic)	**30(31.6%)**	**65(68.4%)**	**1.2**	**0.661-2.18**	0.545
Group (concomitant)	**35(35.7%)**	**63(64.3%)**			

Adverse Events

Severe side effects was seen in 17.9% (N=17) of patients in classic group and 30.6% (n = 30) of patients in Con-5 group over the treatment period; this difference was statistically significant (P value= 0.045). The most common complications in the Classic group were abdominal pain , bad oral taste, and the most common complications observed in Con-5 group were abdominal pain, bad oral taste and nausea. Although abdominal pain was the most common complication encountered in both groups, but there was no statistical significant difference between the two groups in terms of abdominal pain [P value = 0.676]. Other medical complications are presented in Table 3.

Table 3. Adverse Events in the triple therapy and 5-days concomitant therapy

Variables		Classic Group N (%)	5-days concomitant Group N (%)	P value
Nausea	Yes	6(6.3%)	4(4.1%)	0.533
	No	89(93.7%)	94(95.9%)	
Vomiting	Yes	2(2.1%)	3(3.1%)	0.999
	No	93(97.9%)	95(96.9%)	
Diarrhea	Yes	6(6.3%)	0(0)	0.013
	No	89(93.7%)	98(100%)	
Abdominal pain	Yes	14(14.7%)	12(12.2%)	0.676
	No	81(85.3%)	86(87.8%)	
Constipation	Yes	2(2.1%)	0(0)	0.241
	No	93(97.9%)	98(100%)	
Anorexia	Yes	10(10.5%)	0(0)	*0.001*
	No	85(89.5%)	98(100%)	
Headache	Yes	3(3.2%)	1(1%)	0.363
	No	92(96.8%)	97(99%)	
Bad taste	Yes	10(10.5%)	11(11.2%)	0.999
	No	85(89.5%)	87(88.8%)	
Total advers event		30(30.6%)	17(17.9%)	*0.045*
Patients who withdrew		5(5.2%)	2(2.1%)	0.075
Adherence to-therapy		95(100%)	98(100%)	0.541

Adherence

The adherence in classic group and Con-5 group were respectively, 95% and 98%, and there was no statistically significant difference between the two groups. (P value =0/541)

The factors that affect the eradication of H. Pylori infection

Factors which may affect the eradication of H. pylori were investigated using multiple logistic regression analysis. Based on the results of multi-variant analysis, factors such as age, sex, education, smoking, and alcohol consumption have no effect on the eradication of H. Pylori.

DISCUSSION

This clinical trial was conducted aimed to compare the effectiveness of triple therapy regimen and 5-days concomitant regime. Our findings showed that the eradication rate of H. pylori using triple therapy regimen is higher than Con-5. The differences between the two regimens was not statistically significant (P value = 0.545). In our study, H. pylori eradication rate using triple therapy was obtained as 68.4% using the PP analysis and 65% using ITT analysis. However the eradication rate of H. Pylori using Con-5 regimen was 64.3% and 63 percent respectively, using the ITT and PP analysis methods.

Our study shows that there is no significant difference between eradication rate using the triple therapy regime and Con-5 regime. Our results differ from other studies [12,13,14]. In the study of Naghara and colleagues in Japan eradication rate in concomitant regime was 98.1% [10]. The cause of lack of consistent results with these studies could be due to differences in the rate of resistance to clarithromycin [14,15]. Another reason may be

the Proton Pump Inhibitor (PPI) type used in the treatment regime [16]. A further justification for the lack of consistent between the results is the imidazole type used in the study.[17]Some 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].

Recent studies on the effect of PPI used in the eradication of H. pylori show that the use of new-generation S-omeprazole like Rabeprazole makes access to higher levels of eradication rate possible [16,18,19].

On the other hand, our results are consistent with some studies [20,21,22,]. Gisbertand colleagues in Latin America reported efficacy of 5-days concomitant day regime as 78.7% [9]. In recent years a significant reduction has been observed in the success rate of h. pylori eradication with triple therapy that researchers found increased resistance to metronidazole and clarithromycin as one of the main reasons for it [1, 3,23]. The resistance to clarithromycin in Iran has increased from 4.1% in 1997 to 5.26% in 2013 [24].

Based on the results of this study, the rate of side effects in the Con-5 group was more than Classic group (P value = 0.045). The most common side effects of classic group are abdominal pain(14.7 %) , anorexia (10.5 %), and bad oral taste (10.5 %) and the most common advers events of Con-5 group were abdominal pain(12.2 %), bad oral taste(11.2 %) and nausea(4.1 %) . The results of this study were different from the results of most studies .The majority of studies suggest that there is no statistically significant difference between treatment groups [15,19,23,24].

This study showed that, the eradication rates using classic triple therapy and concomitant therapy were not significantly affected by age,sex, education level , alchol consumption and smoking habit. Therapeutic regimen was the only factor that influenced on eradication rate. This result is consistent with other previous studies.[19,23,25,26].

The main limitation of our study is that the resistance to antibiotics has not been evaluated. Another limitation of this study is the small number of subjects. We hope that in the future more studies be conducted with high volume of samples.

CONCLUSION

There was No significant difference between the effectiveness of triple therapy and 5- days concomitant regimes. The effectiveness of both regimes was lower than expected. Using these regimens as first line of treatment of h. Pylori infection is not recommended. Further studies with large numbers of samples in different parts of the country are needed to be conducted for further evaluation of these regimens.

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