Original Article

Two-week Triple Therapy has a Higher *Helicobacter pylori* Eradication Rate Than 1-week Therapy: A Single-center Randomized Study

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ABSTRACT

Background and Aim: To evaluate a high effective and practical regimen for the eradication of *Helicobacter pylori* infection. **Patients and Methods:** The 298 patients with *H. pylori* infection, diagnosed by biopsies performed during the endoscopy, were randomized into two groups. Group 1: Treated for one week with a combination of omeprazole, amoxicillin, and clarithromycin (OAC), named by OAC-1 group ($n = 143$); Group 2: OAC-2 group ($n = 155$) treated for two weeks with OAC. The OAC-1 group was treated with triple therapy of omeprazole 20 mg, amoxicillin 1000 mg, and clarithromycin 500 mg bid for 1 week. OAC-2 group was treated likewise, but for two weeks. A ^{13}C-urea breath test was used to monitor *H. pylori* after four to eight weeks following therapy. **Results:** The eradication of infection was 55% and 68% in the OAC-1 and OAC-2 groups, respectively. Moreover, the eradication rates in the two groups were 63% and 75%, respectively. Compared with the OAC-1 group, the efficacy of treatment in the OAC-2 group is significantly higher ($P < 0.05$). **Conclusion:** Two-week OAC regimen yields a higher eradication rate of *H. pylori*, which might be a practical regimen for the eradication of *H. pylori*.

Key Words: Eradication, *Helicobacter pylori*, intention-to-treat analysis, per-protocol analysis

How to cite this article: Wang J, Zhang G, Hu X, Liu Y, Bao Z, Huang Y. Two-week triple therapy has a higher *Helicobacter pylori* eradication rate than 1-week therapy: A single-center randomized study. Saudi J Gastroenterol 2015;21:355-9.

Helicobacter pylori infection was approved to be the certain biological factor in the pathogenesis of several upper gastrointestinal diseases, including gastritis, gastric ulcer, and gastric carcinoma. *H. pylori* eradication was required in many conditions.[1] The standard triple therapy as the firstline of treatment to *H. pylori* infection is based on proton pump inhibitors (PPI), clarithromycin, and amoxicillin or metronidazole. The therapeutic time spans from 7 days to 2 weeks. Among them, the 7-day PPI-based triple therapy is widely accepted and conducted. However, the length of treatment course on therapeutic effect is uncertain. The prevalence region and the human race affect *H. pylori* eradication to a great extent. And the reports that came from China are relatively few.

This study analyzed a sample of 298 patients using triple therapy in China, aiming to figure out the efficacy difference between 7-day and 14-day therapy. Meanwhile, we try to find out other possible factors that may influence *H. pylori* eradication.

MATERIALS AND METHODS

Study design

This was a prospective, single-centered, randomized, single-blind, controlled study. All the eligible patients were given a standard triple treatment of omeprazole (20 mg, bid), clarithromycin (500 mg, bid), and amoxicillin (1 g, bid) and were randomly divided into 1-week group (OAC-1) or 2-week group (OAC-2) according to random number table. *H. pylori* eradication was assessed in both groups by

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Quick Response Code:

Website: www.saudijgastro.com

DOI: 10.4103/1319-3767.170951

endoscopy or urea breath test (UBT) two months after the eradication.[2]

Besides investigation of the difference in eradication rate between the two groups, other possible influential factors including age and gender were evaluated. In addition, the compliance and adverse effects were also compared between the two groups.[3]

Study population

The study was conducted at Huadong Hospital affiliated to Fudan University, Shanghai, China. The hospital was a tertiary-care center. Nearly all the patients are native Chinese. This study included outpatients (from October 2009 to October 2010) who were diagnosed with *H. pylori* infection by endoscopy or UBT. All the patients were carefully interviewed by physicians. The exclusion criteria were as follows: (1) Patients who used to receive *H. pylori* eradication treatment, (2) patients who took bismuth, PPIs, H2-receptor blockers, and antibiotics in the previous 1 month, (3) patients who were allergic to the drugs included in the study, (4) patients who were pregnant or breast-feeding. The study was approved by the Ethical Board of Huadong Hospital. Written informed consent was obtained from all the patients at enrolment.[4]

Patients were further categorized into three groups by their manifestation, medical history, and endoscopic diagnosis. Firstly, endoscopic findings of peptic ulcer are categorized into peptic ulcer disease (PUD) group. Secondly, endoscopic findings of nonulcer but indication of gastroesophageal reflux or clinical complaint of vomiting and heartburn were categorized into gastroesophageal reflux disease (GERD) group. Finally, the remaining patients enrolled were categorized into NUD (Non Ulcer Dyspepsia) group.

The method of *H. pylori* infection

H. pylori infection was tested by rapid urease test (RUT) during endoscopy or ^{13}C-UBT, and the results were reported by Ji Danian and Liu Xuejing, respectively. Negative results in RUT or ^{13}C-UBT 2 months after the eradication treatment are defined successful in eradication treatment.[5]

Compliance and tolerance

Less than 10% of all the prescript drugs returning after finishing the treatment were designated as good compliance. Severe adverse reactions were recorded in the daily report forms, which were obtained in 1 week after the treatment. The adverse effects included (1) mild: Nausea; (2) moderate: Vomit and diarrhea; (3) Severe: Allergy.[6]

Sample size and statistical analysis

Sample size estimation was carried out according to look-up table method 6. Both groups of estimated sample size were 130 when the sample size of OAC-1 group was similar to OAC-2 ($\alpha = 0.05$, $\beta = 0.1$, $P_{minor} = 0.3$, $\delta = 0.2$).

The data were analyzed for intention-to-treat (ITT) and per protocol (PP). ITT analysis includes all the patients who were enrolled into the investigation at the beginning. PP analysis excludes those who missed the follow-up visit or quit in case of severe adverse effects. Chi-square test or *t* test were used to analyze the data. A multifactor logistic including age, smoking, gender, treatment, and disease group were included in the pattern (Spss18). For all tests, a $P < 0.05$ was considered as statistically significant.

RESULTS

Patient population

Of the 298 *H. pylori*-positive patients enrolled in the study, PUD was diagnosed in 99, 75% of whom with duodenal ulcer; NUD in 92; and GERD in 47, 27% of whom with erosive esophagitis. A total of 143 patients were randomized to OAC-1, 155 to OAC-2, and the two groups showed comparable demographic and clinical characteristics [Table 1].

All patients were considered for ITT analysis, but only 267 for PP analysis, the 31 patients (10.4%) being excluded as therapy had been withdrawn due to severe adverse effects ($n = 11$) or patients had been lost to follow-up or showed poor compliance ($n = 11$). The difference of the incidence of dropouts between the OAC-1 group (11.89%) and the OAC-2 group (9.03%) was no significant. Among the dropout patients, there were six and five patients due to severe adverse effects in the OAC-1 group, and in the

Table 1: Demographic and clinical features of 298 *Helicobacter pylori*-positive patients enrolled in study

Feature	1-Week OAC (*n*=143)	2-Week OAC (*n*=155)	Chi-square value/ *t* value	*P*
Gender (male/female) *n* (%)				
Male	66 (46.15)	76 (49.03)		
Female	77 (53.85)	79 (50.97)	0.619	0.082
Age (years, mean±SD)	51.4±11.4	53.0±13.5	1.120	0.264
Smoker *n* (%)				
Yes	33 (23.08)	38 (24.52)		
No	110 (76.92)	117 (75.48)	0.085	0.771
Disease *n* (%)				
PUD	52 (36.36)	47 (30.32)		
NUD	74 (51.75)	78 (50.32)		
GERD	17 (11.89)	30 (19.35)	3.476	0.176

PUD: Peptic ulcer disease, NUD: Non ulcer dyspepsia, GERD: Gastroesophageal reflux disease, OAC: Omeprazole, amoxicillin, and clarithromycin

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Volume 21, Number 6
Muharram 1437H
November 2015

The Saudi Journal of
Gastroenterology

OAC-2 group, respectively, and the difference between the two groups was not significant (*P* = 0.657).

Eradication rates

H. pylori eradication rates, according to the two regimens, are shown in Table 2. At ITT analysis, OAC-2 (67.09% with 95% CI of 52.30%–81.88%) was found to be significantly more effective compared with OAC-1 (55.94% with 95% CI of 39.67%–80.94%) (*P* = 0.048). According to the PP analysis, the difference was not significant between OAC-2 eradication rate (73.76% with 95% CI of 57.81%-88.28%) and OAC-1 (63.49% with 95% CI of 46.68%-80.30%). At one-factor analysis, 2-week regimens showed a trend toward a significantly higher efficacy than the 1-week regimens according to ITT criteria (OR: 1.44 with 95% CI of 1.10-2.84, *P* = 0.018), and were significantly effective at PP analysis (OR: 1.79 with 95% CI of 1.06%-3.03%, *P* = 0.029). No significant differences were found as far as age, gender, and type of disease, either at ITT or PP analysis [Table 3] is concerned. The multifactor logistic regression model was adopted both for the ITT and PP analyses [Table 4].

Antibiotic combination and duration of therapy resulted as independent factors correlated with the eradication of *H. pylori* infection. The eradication rate achieved with OAC-2 regimens was significantly higher than that with OAC-1 regimens at ITT but not at PP analysis. The 2-week duration of therapy was associated with a higher rate of *H. pylori* eradication at ITT analysis. Gender, age, type of disease, and smoking habit had no influence on eradication rates [Table 4].

DISCUSSION

Because of the increasing rate of drug resistance and lack of absolute superior antibiotics, eradication research focuses on all kinds of regimes.[7,8] Besides standard 7-day triple therapy, there are 10-day, two weeks, and corresponding sequential therapies. Lushan Conference in China in 2007 advocated that 14-day therapy is superior to 10-day and 7-day therapies.[9] The results of sequential therapy are inconsistent. Many clinical researches reported that it is superior to 7-day or 10-day therapies, even better than

Table 2: *Helicobacter pylori* eradication rates calculated according to intention-to-treat and per-protocol analyses

Regimen	No. of patients	No. of drop-outs (%)	ITT analysis % (95% CI)	PP analysis % (95% CI)
OAC-1	143	17 (11.89)	55.94 (39.67-80.94)	63.49 (46.68-80.30)
OAC-2	155	14 (9.03)	67.09 (52.30-81.88)[a]	73.76 (57.81-88.28)
PUD	99	11 (11.11)	64.64 (45.80-83.48)	72.73 (54.12-91.34)
NUD	152	16 (10.53)	59.87 (44.29-75.45)	66.91 (51.09-82.73)
GERD	47	4 (8.51)	61.70 (33.90-89.50)	67.44 (39.43-95.45)

ITT: Intention-to-treat, PP: Per-protocol, PUD: Peptic ulcer disease, NUD: Non ulcer dyspepsia, GERD: Gastroesophageal reflux disease, OAC: Omeprazole, amoxicillin, and clarithromycin. [a]Chi-square test, *P*=0.048

Table 3: One-factor analysis: Prognostic factors associated with *Helicobacter pylori* eradication

Prognostic factors	ITT analysis				PP analysis			
	χ^2	*P*	OR	95% CI	χ^2	*P*	OR	95% CI
2 weeks vs 1 week	5.58	0.018	1.77	1.10-2.84	4.74	0.029	1.79	1.06-3.03
Gender (male/female)	2.91	0.088	0.66	0.42-1.06	1.71	0.191	0.71	0.42-1.19
Age (≤50 vs >50 years)	0.675	0.411	0.82	0.51-1.31	0.88	0.347	0.78	0.46-1.31
Smoke (yes/no)	2.88	0.089	0.63	0.37-1.08	1.80	0.179	0.66	0.36-1.21
PUD vs NUD	0.19	0.661	1.23	0.73-2.07	0.48	0.490	1.32	0.73-2.38
GERD vs NUD	0.04	0.842	1.18	0.60-2.33	0.00	0.986	1.14	0.54-2.40

ITT: Intention-to-treat, PP: Per-protocol, PUD: Peptic ulcer disease, NUD: Non ulcer dyspepsia, GERD: Gastroesophageal reflux disease

Table 4: Multifactor logistic analysis: Prognostic factors associated with *Helicobacter pylori* eradication

Prognostic factors	ITT analysis				PP analysis			
	OR	95% CI	χ^2	*P*	OR	95% CI	χ^2	*P*
Gender (male/female)	0.72	0.40-1.28	1.28	0.259	0.75	0.40-1.42	0.78	0.376
Smoke (yes/no)	0.72	0.37-1.40	0.93	0.333	0.72	0.35-1.51	0.74	0.390
PUD vs NUD	1.39	0.81-2.38	1.07	0.301	1.48	0.80-2.74	1.49	0.222
GERD vs NUD	1.07	0.53-2.14	0.08	0.775	1.01	0.47-2.15	0.26	0.612
Age (≤50 vs >50 years)	1.14	0.70-1.85	0.27	0.602	1.22	0.71-2.08	0.50	0.478
2 weeks vs 1 week	1.80	1.11-2.93	5.66	0.017	1.79	1.04-3.06	4.43	0.353

ITT: Intention-to-treat, PP: Per-protocol, PUD: Peptic ulcer disease, NUD: Non ulcer dyspepsia, GERD: Gastroesophageal reflux disease

14-day therapy, and it can provide alternative regime in case of drug resistance. But the effectiveness of sequential therapy can also decrease due to drug resistance, which indicates the cause of the unsatisfied reality of application in recent years.[10,11] A recent report showed that sequential and standard triple therapies were similarly effective at eradicating *H. pylori* in two-thirds of Saudi patients.[12] The follow-up studies show that in some countries, such as Italy, in the same period there are areas with unchanged efficacy of the OAC regimen[13] and area with a relevant decreasing efficacy.[14] Most of these recommendations are based on PPI combined with amoxicillin or metronidazole.[15] With increasing drug resistance of firstline antibiotics to *H. pylori*, an assessment on the efficacy and advantage of 14-day triple therapy after all these application years is necessary.

In this study, we compared 14-day with 7-day triple therapy of OAC. We also did other comparisons as drug resistance to *H. pylori* may be associated with smoking, gastric diseases, or some other factors.[16,17]

The result shows that 14-day therapy is superior to 7-day therapy in ITT analysis. The therapeutic effectiveness in patients with GERD is superior than those with NUD.[18,19] Mamori reported that age can influence the eradication rate. The eradication rate in patients younger than 50 years is lower than those older than 50 years. But in our study, the eradication rate showed no statistical difference between these two groups. There was also no influence of age (data not shown) in the study. This can be explained by difference in compliance.[9,20]

OCA is obviously not the best therapy to those who are resistant to clarithromycin. This may greatly influence those results of the investigation using clarithromycin. According to various reports, clarithromycin resistance varies remarkably in different geographic areas. The rates of Europe (11.1%), Asia (18.9%), and America (29.3%) significantly differ.[3,11] According to Gao, the resistant rate of *H. pylori* to clarithromycin has reached 35% in Peking area; according to Sun, from the year 2000 to 2009, it has increased from 9.0% to 20.7% in Shanghai.[20] In a prospective multiregion study on primary antibiotic resistance of *H. pylori* isolated from Chinese people, the clarithromycin resistance rate has reached up to 37.5%,[21] which indicated that the resistance rate may be unexpectedly high in the metropolis areas due to the wide use of clarithromycin in respiratory diseases. Resistance to clarithromycin may even reduce the eradication rates up to 70%. Not surprisingly, the eradication rate in this report is relatively low, and it is lower than several recent reports of eradication therapy using clarithromycin.[21] This enhances the necessity of further research in drug resistance of *H. pylori* strains in particular populations.[1,22] In addition, the current result has several limitations. We excluded the patients with amoxicillin

hypersensitivity in advance and the triple therapy is simply based on omeprazole, amoxicillin, and clarithromycin. These may cause some bias in the result.[20] The data of adverse reaction gathered is incomplete, but this article focuses on the happening situation because of the severe adverse effects. The results show that the difference between the two groups was not significant ($P = 0.657$), six and five patients due to severe adverse effects in the OAC-1 group and in the OAC-2 group, respectively. This could suggest that there may be no significant difference between the side effects seen in OAC-1 and OAC-2 in a way.

CONCLUSION

A fourteen-day OAC triple therapy for *H. pylori* eradication is significantly more effective than 7-day therapy. But considering the relatively low eradication rate compared with the international guideline recommendation from the 3rd Maastricht Consensus Report for effective treatment of *H. pylori*, the OAC regimen may give way to other drug combinations.

Financial support and sponsorship

Conflicts of interest
All authors declare that they have no potential conflicts of interest.

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