Jundishapur Journal of Natural Pharmaceutical Products 2008; 3(1): 45-52

Jundishapur Journal of Natural Pharmaceutical Products

COMPARISON OF A 10 DAY TRIPLE AND A TWO-WEEK QUADRUPLE THERAPY IN ERADICATING *HELICOBACTER PYLORI* INFECTION IN PATIENTS REFERRED TO IMAM KHOMEINI HOSPITAL CLINICS AHWAZ, IRAN

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Received: 18 May 2008 ***Accepted: 10 March 2009***

Abstract

Helicobacter pylori eradication has become the standard treatment for peptic ulcer disease. It is also indicated in cases with atrophic gastritis, and following gastric cancer resection. Many short-term (one week) triple therapy regimens suffer from the problem of resistance. The aim of the present study was to evaluate the clinical efficacy and safety, patient compliance and tolerability of a 10 days triple therapy versus 2 week conventional therapy in patients with peptic ulcer disease or chronic gastritis in eradicating *Helicobacter pylori* infection. A total of 160 *H. pylori*-positive patients suffering from peptic ulcer disease or chronic gastritis without previous treatment were enrolled in the study and randomly allocated into the following two groups: group A (n = 85) received a 2 week quadruple therapy regimen using omeprazole, amoxicillin, bismuth subcitrate and metronidazole (BOMA); group B (n = 75) received a 10-d triple therapy 20 mg omeprazole b.i.d., 1000 mg amoxicillin b.i.d., 500 mg clarithromycin b.i.d. (OAC), (before breakfast and dinner). Eradication verified with UBT technique 8 weeks after completion of the therapy. Three cases were lost to follow-up one from group A (B-OAM) and two cases from group B (OAC). H. pylori eradication rates produced by B-OAM and OAC were 61% and 78% respectively based on an intention to treat analysis, and 63% versus 81% respectively based on a per-protocol analysis. The triple protocol yielded higher eradication rate by both per-protocol and intention-to-treat analyses. 10 day triple therapy regimen achieves an H. pylori eradication rate superior to that of a 2-week quadruple therapy and is associated with comparable patient compliance and complications but we achieved relatively low eradication rates and further investigations are needed in Khuzestan area.

Keywords:

Helicobacter pylori, Triple therapy; Quadruple therapy, Khuzestan, Iran.

Introduction

Since the first evidence emerged in 1983, further evidence has accumulated that *Helicobacter pylori* (*H. pylori*) plays a major pathogenetic role in peptic ulcer disease (1). A meta-analysis study has shown that *H. pylori* eradication reduces peptic ulcer recurrence (2).

Iran is one of those countries where *H. pylori* infection is the most prevalent in the World. The estimated prevalence of *H. pylori* infection is approximately 65% in this country (3). Therefore, *H. pylori* infection is a significant health problem.

Eradication of *Helicobacter pylori* infection has become a wide clinical

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practice for *H. pylori* related diseases, but the results obtained appear to be controversial (4-5).

However, many short-term (one week) triple therapy regimens suffer from the problem of resistance, which could significantly decreases clinical efficacy (6-8). Therefore, it is a very important issue to search for anti-*H. pylori* regimens that are highly effective in eradicating *H pylori* infection but without drug resistance (9).

The aim of the present study was to compare the efficacy of two standard first-line eradication regimens, in patients with peptic ulcer disease or chronic gastritis in eradicating *Helicobacter pylori* infection in south of Iran.

Materials and methods

A total of 160 consecutive dyspeptic patients, diagnosed *H. pylori* positive at endoscopy (88 male and 72 female subjects, median age 39.2 years) referred and observed in our Center for a 2-year period were considered eligible for the study.

This study protocol was approved by the institutional Ethics Review Committee, and each patient signed an informed consent.

Selection of patients

Criteria of selection (1) those aged 18-70 years. (2) Patients with peptic ulcer (DU or GU) or chronic gastritis (CG) confirmed by gastroscopy. (3) Those were positive for *H. pylori* by a rapid urease test (RUT) and positive by serology, silver or Giemsa staining and histological examination.

Criteria of exclusion (1) Patients who had gastric cancer or severe gastroesophageal reflux disease, or gastric operation history. (2) Patients who were in lactation or pregnancy. (3) Patients who had combined severe diseases of other system that might affect the medical evaluation of this study. (4) Patients who took the drugs included in this study over the past month. (5) Patients who were allergic to the drugs.

Drugs Regimen

group A (*n*= 85) received a two-week quadruple therapy regimen using Omeprazole (20mg), metronidazole (500mg), amoxicillin (1000mg) bismuth subcitrate (240mg) and (BOMA). Each patient took the drugs twice a day for 14 days.

group B (*n* = 75) received a 10-day triple therapy 20 mg omeprazole b.i.d., 1000 mg amoxicillin b.i.d., 500 mg clarithromycin b.i.d. (OAC);. (Before breakfast and dinner).

Procedures

At the entry, clinical symptoms, demographic data and medical history were recorded, and gastroscopy was performed to establish the endoscopic diagnosis and status of *H. pylori* infection. During the gastroscopy examination, four biopsy specimens were taken from stomach: one for a rapid urease test (RUT), one for silver or modified Giemsa staining, and two for histological examination. Serum anti-*H. pylori* IgG antibodies were also detected. The patients who were intensive positive by the RUT (positive in five minutes) were initially considered to be qualified for the study. Only those patients who were also positive by serology, *H. pylori* staining and histological examination were included in the clinical trial. Patients were followed up on the eighth day to check clinical symptoms, side effects and compliance.

Definition of H. pylori eradication

H. pylori eradication was defined when the urea breath test was negative (negative UBT) 8 weeks after completion of anti-*H. pylori* therapy.

Results

Demographic and clinical data

Of the 160 patients enrolled in the study, 157 (98.1%) completed the treatment and three (1.9%) dropped off, one case from group A (BOAM) and two cases from group B (OAC). Consequently, 157 patients were included in PP analysis.

Among 157 patients 88 were male (54.8%) and 72 female (45.2%) subjects and the mean age was 39.2 years.

Of these, 85 patients were randomized to the BOMA group and 75 patients to the OAC group.

There were nearly six times more duodenal ulcers than gastric ulcers. The primary endoscopy found 51 active ulcers, all of which were positive for *H. pylori* infection. Upper endoscopy revealed that 86 % of the patients had duodenal ulcers and 14 % had gastric ulcers (a 6:1 DU: GU ratio). Since the active ulcers were in duodenal area, therefore upper endoscopy after treatment was not necessary. The breath test was considered to be enough for patients.

Demographic characteristics were not significantly different between the two groups (Table 1).

The *H. pylori* eradication rate of BOMA group was lower than that of OAC group in both ITT and PP analyses. 63.5% and 82.6% respectively based on an intention to treat analysis, and 64.2% versus 84.9% respectively based on a per-protocol analysis. (Table 2).

Minor adverse effects were experienced by 11 patients in group BOMA and 6 patients in group OAC (13%versus 8.2%) but intolerability was similar in the two groups (95% versus 93.2%). The symptoms were mild and did not necessitate any additional treatment for severe complications.

However, the differences were not statistically significant between the two groups (p = 705) (Table 3).

Statistical analysis

Demographic characteristics between the two groups were compared by the chi-squared test. The *H. pylori* eradication rates were assessed by intention-to-treat analysis (ITT analysis) and per-protocol analysis (PP analysis).

Table 1. Demographic characteristics of two groups

	OAC group	BOMA group
Total number of patients	N=75	N=85
Dropped out patients	2	1
Completed study	73	84
Male	45	42
Female	30	43
D. U.	21	23
G. U.	3	4
Active ulcers	24	27

OAC= omeprazole, amoxicillin, clarithromycin
BOMA= bismuth subcitrate ,omeprazole, amoxicillin, and metronidazole
D. U= duodenal ulcer
G. U= gastric ulcer

The differences of *H. pylori* eradication rates between two groups and their 95% confidence intervals (CI) were calculated in both ITT and PP analyses.
We also compared the incidences of adverse events between two groups using the chi-squared test. *P* -values < 0.05 were considered to be statistically significant. Statistical analysis was performed using SPSS for Windows (version 12.0; SPSS Inc., Chicago, IL, USA).

Discussion

In 1990, the 14-day bismuth triple therapy was recommended in the Ninth World Gastroenterology Conference in Sydney (10). Much controversy exists in the published reports concerning which regimen for *H. pylori* eradication should be administered in order to obtain the maximal eradication rate (10-11).
Actually, the antibiotic resistance rate is reported to be increasing in Iran recently (12).
It has been reported that prevalence of metronidazole resistant *H. pylori* strains has increased to more than 30-72% in Iran and other countries (13-15).
Due to its high incidence of failure of *H. pylori* eradication with metronidazole triple therapy, this regimen has been replaced with other triple therapy or quadruple therapy regimens (15-16, 3). However, with the wide application of anti-*H. pylori* therapy and antibiotic abuse, mainly relates to treatment of parasite infection, dental infection and gynecological diseases, the eradication rates with those regimens decreased due to emergence of metronidazole resistance in *H. pylori* over the past few years (17).

Table 2. Eradication of H. pylori and treatment results in OAC and BOMA groups

	OAC group	*BOMA group*
Total number of patients	N=75	*N=85*
Dropped out patients	2	*1*
Compliance	(97%) 73/75	*(98%) 84/85*
Treatment failure	13	*31*
Adverse effects	8.2%	*13 %*
Eradication rate(ITT)	82.6%	*63.5%*
Eradication rate(PP)	*84.9%*	*64.2%*

ITT= intention-to-treat analysis
PP= per-protocol analysis

Table 3. Adverse events of both groups during treatment period

Frequency of adverse events	OAC group	BOMA group
Gastroenteric reactions	3	3
Skin eruption	0	2
Dizziness	2	3
Glossitis	0	0
Weakness	1	0
Anorexia	0	5
Total	N=6	N=11

OAC= omeprazole, amoxicillin, clarithromycin.
BOMA= bismuth subcitrate ,omeprazole, amoxicillin, and metronidazole.

At present the resistance to clarithromycin in *H. pylori* is diverse in the world. South-north difference existed such as the drugs used to treat other infection before (mainly respiratory infection) (18). Clarithromycin is widely used in current clinical practice in Iran. Accordingly, *H. pylori*-infected patients with initial resistance to clarithromycin are growing year by year (13, 19). This has led to concerns on the increasing number of patients with poor response to the first-line *H. pylori* eradication therapy. Some recent studies have compared the efficacy of triple versus quadruple therapy, and a recent meta-analysis has assessed these studies (20). The *H. pylori* eradication rate of clarithromycin based triple drug regimen was 76-90% in western countries (21) whereas in Iran this rate was lower, possibly due to increasing rate of drug resistance. In a recent study performed the *H. Pylori* eradication rates was about 73.1% (13).

Most studies in Iran failed to show correlation between ages, gender, duration of the symptoms, or smoking habits, with *H. Pylori* eradication. Some studies indicated that patients of more than 42-years-old had better prognostic indication factors for *H. Pylori* eradication (22-23). Other factors such as socioeconomic condition and geographical situation were not considered in these studies (23).

In order to evaluate of the clinical efficacy and safety of a two-week quadruple and a clarithromycin based triple drug regimen in eradicating *Helicobacter pylori* infection, we carried out this study. Our region is Khuzestan in southern of Iran consists of several cities, with 3 million inhabitants. The male-female ratio in our study is approximately 1.2:1 (88 males and 72 females) However, this difference did not significantly affect the eradication rates, nor did the age (p = 705). The mean age of our patients was 39.2 years, which is a little lower than what was found in other studies (44 to 50 years) (24). Theoretically, this could represent early infection, due to the living conditions of our population.

There were nearly six times more duodenal ulcers than gastric ulcers. The primary endoscopy found 51 active ulcers, all of which were positive for *H. pylori* infection.

The *H. pylori* eradication rate of BOMA group was lower than that of OAC group in both ITT and PP analyses. 63.5% and 82.6% respectively based on an intention to treat analysis, and 64.2% versus 84.9% respectively based on a per-protocol analysis.

Minor adverse effects were experienced by 11 patients in group BOMA and 6 patients in group OAC (13%versus 8.2%) but intolerability was similar in the two groups (95% versus 93.2%). The symptoms were mild and did not necessitate any additional treatment for severe complications. However, the differences were not statistically significant between the two groups (p = 705) (Table 3).

The treatment regimens with eradication rate of 90% or greater by per-protocol analysis have been recommended for *H. pylori* infection (25). However, our study shows that the current OAC triple regimen and BOMA quadruple regimens cannot achieve an eradication rate of up to 90% in our study groups, which is maybe due to antibiotic resistance, so the H. *pylori eradication* rates of both treatment regimens are not satisfactory here. Accordingly, the new combination regimen containing alternative antibiotics that shows higher eradication rate than these regimens may be the promising first-line treatment for *H. pylori* infection in our area.

Although the incidences of adverse events were not significantly different between the two groups, the cost of OAC triple regimen is much higher than that of BOMA quadruple regimen.

Since the cost of this triple therapy is high and the *H. pylori* eradication rate of both BOMA and OAC regimens is low, new combination regimen with higher eradication rate for *H. pylori* should be developed and tested in south of Iran. There have been reports of excellent results acquired by *H. pylori* eradication using clarithromycin and furazolidone based quadruple regimen with an optimal eradication rate of 92% (23). Such regimens had significant side effects up to 62% of the patients.

We may recommend that BOMA and OAC regimens be replaced by a clarithromycin or furazolidone-based quadruple regimen for a minimum duration of two weeks in our area, but the patients should be monitored for side effects of these regimens.

In conclusion, OAC *H. pylori* eradication therapy is more effective than BOMA quadruple therapy. However, these regimens are well tolerated but, *H. pylori* eradication rates of both treatment regimens are not satisfactory, which suggests decreasing eradication rate due to increasing antibiotic resistance rates.

A search for an alternative new combination regimen with higher eradication rate for *H. pylori treatment* should be developed and tested in south of Iran.

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