



Randomized Controlled Trial

## Seven-day quintuple regimen as a rescue therapy for *Helicobacter pylori* eradication

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regimens for eradication of *Helicobacter pylori* (*H. pylori*) in patients who failed previous therapies.

**METHODS:** This prospective, open-label, randomized controlled trial was a phase II study conducted from April 2011 to March 2012 at the Gastrointestinal and Liver Diseases Research Center in Rasht, Iran. A total of 208 patients with dyspepsia who failed previous *H. pylori* eradication with a ten-day quadruple therapy were enrolled. A random block method was used to assign patients to one of two treatment groups. Patients in the first group were treated with 240 mg bismuth subcitrate, 20 mg omeprazole, 1000 mg amoxicillin, 500 mg clarithromycin and 500 mg tinidazole (BOACT group). Patients in the second group received a regimen containing 240 mg bismuth subcitrate, 20 mg omeprazole, 500 mg tetracycline, 500 mg metronidazole and 200 mg ofloxacin (BOTMO group). Both regimens were given twice daily for a duration of seven days. The eradication was confirmed by a <sup>14</sup>C urea breath test 12 wk after completion of therapy. Patient compliance and drug side effects were evaluated at the end of the treatment period. The success rates were calculated by intention-to-treat and per-protocol analyses.

**RESULTS:** A total of 205 patients completed the course of treatment, with three patients excluded due to drug intolerance. The mean age of patients did not differ between the BOACT and BOTMO groups (41.6 ± 12.2 years vs 39.6 ± 11.8 years), and no significant differences were found between the two groups in terms of age, sex, smoking habits or the initial eradication regimen. The intention-to-treat and per-protocol eradication rates were significantly higher in the BOTMO group (86.5%, 95%CI: 0.85-0.87 and 86.7%, 95%CI: 0.80-0.89, respectively) compared with the BOACT group (75.5%, 95%CI: 0.73-0.76 and 76%, 95%CI: 0.69-0.80, respectively) (*P* < 0.05). Univariate analyses for both groups did not show any association of sex, smoking and initial therapeutic regimen with

### Abstract

**AIM:** To determine the efficacy of two quintuple

eradication rate ( $P > 0.05$  for all). Significantly more patients experienced side effects in the BOACT group compared to the BOTMO group (77.4% vs 36.6%,  $P < 0.01$ ). This difference was exemplified by increases in headache and taste disturbance ( $P < 0.05$ ).

**CONCLUSION:** Quintuple therapy with a BOTMO regimen is an alternative second-line rescue therapy for Iranian patients with failed first-line eradication treatment of *H. pylori*.

**Key words:** Antibiotic resistance; Rescue therapy; Eradication; *Helicobacter pylori*; Quintuple therapy

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**Core tip:** Due to increasing antibiotic resistance, eradication of *Helicobacter pylori* has become more challenging. Antibiotic resistance exhibits a regional pattern and treatments typically involve 14-d medication periods, which are not always effective. This study compared two 7-d quintuple regimens and identified a regimen of bismuth subcitrate, omeprazole, tetracycline, metronidazole, and ofloxacin as an effective alternative second-line rescue therapy with minimal side effects for Iranian patients who failed a course of first-line treatment.

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## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) infection is a global health problem associated with chronic gastritis, peptic ulcer disease and gastric cancer, which affects 20%-50% of people in Western nations and up to 80% of the population in developing countries<sup>[1,2]</sup>. Therefore, the eradication of the pathogen is of great importance to reduce *H. pylori*-related complications<sup>[3,4]</sup>. However, treatment failures resulting from antimicrobial resistance and poor compliance have become an increasing concern. This is especially important in regions with a high prevalence of *H. pylori* infection, such as Iran, where the prevalence, re-infection rate and resistance to standard therapeutic regimens are much higher than in Western countries<sup>[4-7]</sup>. Treatment with triple therapy, which is the most frequently recommended, fails to eradicate *H. pylori* in approximately 20% of cases<sup>[8]</sup>. Treatment with quadruple rescue therapy is still insufficient to reduce the failure rate below 20%<sup>[9,10]</sup>. Bacterial culture and microbial susceptibility tests are recommended by European guidelines for selection of third-line treatment regimens,

but these methods are hindered by low sensitivity, high cost, unavailability and their invasive nature<sup>[11,12]</sup>. Therefore, designing a novel rescue regimen that achieves greater than 80% eradication rate is a target of current research<sup>[11,13]</sup>.

Recently, several multidrug rescue regimens against refractory *H. pylori* infection have been studied, though an ideal therapeutic regimen has not yet been identified<sup>[12,14-18]</sup>. In Iran, the most common regimen for the first-line treatment is a 14-d quadruple therapy containing bismuth subcitrate, omeprazole, metronidazole and either tetracycline or amoxicillin<sup>[19]</sup>. Mousavi *et al*<sup>[20]</sup> showed that a 14-d quadruple therapy (including amoxicillin) resulted in an eradication rate of 70.4% based on an intention-to-treat (ITT) analysis, and 75.7% based on a per-protocol (PP) analysis. Similarly, Agah *et al*<sup>[5]</sup> reported a 68% eradication rate using the same regimen. A higher eradication rate of 84% by ITT analysis was reported by Fakheri *et al*<sup>[21]</sup> with quadruple therapy including bismuth subcitrate, omeprazole, amoxicillin and clarithromycin. Despite the benefit, clarithromycin exhibits resistance that varies over time and based on the geographic region. In Iran, there is a high prevalence of clarithromycin and metronidazole resistance, indicating that Western eradication regimens are not ideal in this region<sup>[22]</sup>. Our previous study in an antibiotic-sensitive area of Iran using 7- and 14-d furazolidone-based quadruple regimens failed to show acceptable eradication rates by ITT analysis (71% and 65%, respectively)<sup>[23]</sup>. Therefore, rescue regimens should be chosen based on the regional pattern of antibiotic resistance, taking into account patient compliance, drug efficacy and safety<sup>[5,22]</sup>. The aim of this study was to compare two quintuple rescue therapy regimens with regard to compliance, safety and efficacy in patients who had failed an initial quadruple course of therapy.

## MATERIALS AND METHODS

### Setting

This phase II study was a prospective, open-label, randomized controlled trial conducted from April 2011 to March 2012 at the Gastrointestinal and Liver Diseases Research Center of Guilan University of Medical Sciences, in Rasht, Iran. The study was approved by the ethics committee of the research center, and was in accordance with the Helsinki declaration for use of human subjects. This study is registered in the Iranian Registry of Clinical Trials (identification number: IRCT201103011155N11, Available from: URL: <http://www.irct.ir>).

### Participants

Patients with *H. pylori* infection who failed previous eradication with a ten-day quadruple therapy comprised of bismuth subcitrate, omeprazole, amoxicillin and clarithromycin or bismuth subcitrate, omeprazole, amoxicillin and metronidazole were consecutively recruited for this study ( $n = 208$ ). The patients were referred from the outpatient gastroenterology clinics

and private offices to our referral University center. Twelve weeks after completion of therapy, the diagnosis of *H. pylori* infection was made using a Heliprobe <sup>14</sup>C urea breath test (Kibion AB, Uppsala, Sweden), which shows 94% sensitivity and 100% specificity<sup>[24]</sup>. Patients under 15 or over 65 years of age, and those with co-existing serious illnesses such as liver cirrhosis, uremia and gastrointestinal malignancies were excluded from the study. Other exclusion criteria were pregnancy/lactation and having contraindication or allergy to any of the study drugs. The objectives of the study and potential side effects of drugs were explained to each patient, and informed written consent was obtained.

### Randomization

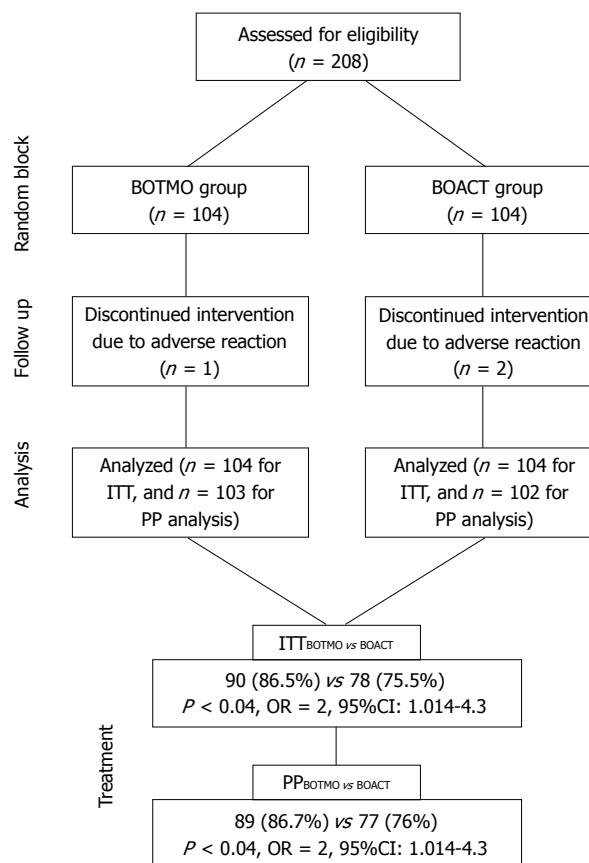
Patients were randomized according to classification guidelines of the Federal Drug Administration/World Health Organization for individually randomized trials for the testing of drugs or devices<sup>[25]</sup>. The random block method was used to assign patients into randomly permuted treatment blocks to ensure an equal number of subjects for each treatment. The first group consisted of 104 patients who received 240 mg bismuth subcitrate, 20 mg omeprazole, 1000 mg amoxicillin, 500 mg clarithromycin and 500 mg tinidazole twice daily for seven days (BOACT group). The second group of 104 patients was treated with 240 mg bismuth subcitrate, 20 mg omeprazole, 500 mg tetracycline, 500 mg metronidazole and 200 mg ofloxacin twice daily for seven days (BOTMO group). Demographic and clinical variables, including age, sex, smoking status and type of previous treatment regimen, were recorded. Patients were instructed to take their prescribed medications at the scheduled times and advised to avoid smoking, drinking alcoholic or caffeinated beverages, eating spicy foods or taking non-steroidal anti-inflammatory drugs or medications containing a monoamine oxidase inhibitor.

### Outcomes

The primary outcome measured was the *H. pylori* eradication rate as assessed by the <sup>14</sup>C urea breath test. Successful eradication of *H. pylori* was confirmed by a negative result. The secondary outcomes were the incidence of adverse effects and patient compliance. Adverse effects from the treatments were assessed using a 0-10 scale system (mild: 0-3, moderate: 4-6, severe: 7-10), and patient compliance was defined as a consumption of > 80% of the prescribed drugs.

### Statistical analysis

ITT and PP analyses were performed to assess the efficacy of the treatment regimens for *H. pylori* eradication. The ITT analysis included all patients who were initially randomized into one of the treatment groups and took at least one treatment dose. The PP analysis excluded patients who refused to continue the treatment, or those with poor compliance to therapy. *H. pylori* eradication percentages, odds ratios and 95%CI were assessed for



**Figure 1** Flow diagram of quintuple therapy comparisons. BOACT: Bismuth subcitrate, omeprazole, amoxicillin, clarithromycin, tinidazole; BOTMO: Bismuth subcitrate, omeprazole, tetracycline, metronidazole, ofloxacin; ITT: Intention-to-treat; OR: Odds ratio; PP: Per-protocol.

each group. Demographic variables, previous treatments, eradication rates, adverse events and patient compliance were compared between the groups using  $\chi^2$  and Student's *t* analyses. Statistical analyses were performed using SPSS, version 16.0 software (SPSS Inc., Chicago, IL, United States), and  $P < 0.05$  was considered to be statistically significant.

## RESULTS

A total of 208 patients with persistent *H. pylori* infection were enrolled in this study. Of the 104 assigned to each group, two patients (females with severe epigastric pain and headache) in the BOACT group and one patient (male with severe nausea) in the BOTMO group were excluded from the study due to drug intolerance (Figure 1).

Basic demographic and clinical characteristics of the study population and their initial eradication therapy regimen are shown in Table 1. The mean age was  $41.6 \pm 12.2$  years for patients treated with BOACT and  $39.6 \pm 11.8$  years for those receiving the BOTMO regimen. Most of the patients were female (BOACT: 72/104, 69.2%; BOTMO: 65/104, 62.5%). No significant differences were found between the two groups in terms of age, sex, smoking habits or initial regimen.

**Table 1** Baseline demographic and clinical characteristics

Characteristic	Regimen	
	BOACT (n = 104)	BOTMO (n = 104)
Male/Female	32/72	39/65
Age (yr)	41.6 ± 12.2	39.6 ± 11.8
Smoking, n (%)		
Yes	28 (26.9)	27 (26.0)
No	76 (73.1)	77 (74.0)
Initial eradication regimen, n (%)		
BOAC	82 (78.8)	75 (72.1)
BOAM	22 (21.2)	29 (27.9)

BOAC: Bismuth subcitrate, omeprazole, amoxicillin, clarithromycin; BOACT: Bismuth subcitrate, omeprazole, amoxicillin, clarithromycin, tinidazole; BOAM: Bismuth subcitrate, omeprazole, amoxicillin, metronidazole; BOTMO: Bismuth subcitrate, omeprazole, tetracycline, metronidazole, ofloxacin.

### Eradication of *H. pylori*

On ITT analysis, the eradication rate was 75.5% (95%CI: 0.73-0.76) in the BOACT group and 86.5% (95%CI: 0.85-0.87) in the BOTMO group; the difference between the two groups was statistically significant (OR = 2, 95%CI: 1.014-4.300;  $P < 0.04$ ). In the PP analysis, *H. pylori* was eradicated in 76% of patients in the BOACT group (95%CI: 0.69-0.80) and 86.7% of patients in the BOTMO group (95%CI: 0.80-0.89); the difference between the two groups was statistically significant (OR = 2, 95%CI: 1.014-4.300;  $P < 0.04$ ).

Univariate analyses for both groups did not show any association of sex, smoking and initial therapeutic regimen with eradication rate ( $P > 0.05$  for all).

### Compliances and adverse effects

Despite the discontinuation of treatment by two patients in the BOACT group and one patient in the BOTMO group, both regimens were well-tolerated by the majority of patients. A total of 71 side effects were reported in 59 patients (28.8%), which were rated as mild (Table 2). A significantly greater proportion of patients reported adverse side effects in the BOACT group compared to the BOTMO group (77.4% *vs* 36.6%;  $P < 0.01$ ). This corresponded with 55 side effects in 35 BOACT patients and 26 side effects in 20 BOTMO patients. Specifically, significantly more reports of headache and taste disturbance occurred in the BOACT group than in the BOTMO group ( $P < 0.05$ ).

## DISCUSSION

The results of the present study show a higher *H. pylori* eradication rate with a 7-d quintuple therapy with BOTMO compared to BOACT in patients who initially failed quadruple therapies. Although both regimens demonstrated good patient compliance, fewer side effects were reported in patients receiving BOTMO therapy. These findings are consistent with those of the only other study comparing the efficacy of a quintuple regimen, comprised of bismuth subcitrate, tetracycline,

**Table 2** Reported side effects n (%)

Side effect	Regimen	
	BOACT (n = 102 <sup>1</sup> )	BOTMO (n = 103 <sup>2</sup> )
Headache	17 (17.6) <sup>a</sup>	7 (7.8)
Taste disturbance	14 (15.7) <sup>a</sup>	6 (5.8)
Nausea	5 (4.9)	3 (2.9)
Epigastric pain	4 (3.9)	2 (1.9)
Diarrhea	4 (3.9)	2 (1.9)
Heartburn	3 (2.9)	2 (1.9)
Stool color change	3 (2.9)	2 (1.9)
Urine color change	2 (1.9)	1 (0.9)
Anorexia	3 (2.9)	1 (0.9)
Total	55 (77.4) <sup>b</sup>	26 (36.6)

<sup>1</sup>Two and <sup>2</sup>one of the patients from the group discontinued treatment due to severe adverse effects. <sup>a</sup> $P < 0.05$ , <sup>b</sup> $P < 0.01$  *vs* control. BOACT: Bismuth subcitrate, omeprazole, amoxicillin, clarithromycin, tinidazole; BOTMO: Bismuth subcitrate, omeprazole, tetracycline, metronidazole, ofloxacin.

metronidazole, roxithromycin and lansoprazole, with triple and quadruple treatment regimens<sup>[26]</sup>. In that study, a significantly higher rate of *H. pylori* eradication was found with the quintuple regimen, though the length of treatment was 14 d and side effects were not evaluated.

At the present, triple therapy suggested by both Canadian and European guidelines is the most preferred first-line regimen in clinical practice<sup>[3,27]</sup>. However, the success rate of this eradication regimen is decreasing<sup>[10,17]</sup>. Even the most commonly recommended quadruple rescue therapy regimen fails to eradicate infection in more than 20% of patients<sup>[6,28]</sup>. In one study of patients with peptic ulcers who failed to respond to previous eradication regimens, an eradication rate of 69% was obtained after treatment with a 7-d course of therapy with bismuth subcitrate, a high-dose of furazolidone (200 mg, b.i.d), amoxicillin and a proton-pump inhibitor<sup>[29]</sup>. A similar eradication rate (63% by ITT analysis) was achieved in another study using a 7-d rescue quadruple regimen containing bismuth subcitrate, omeprazole, tetracycline and a high-dose of furazolidone (200 mg, b.i.d)<sup>[30]</sup>.

Iranian patients show an increasing resistance to metronidazole, clarithromycin<sup>[5,22,23]</sup> and furazolidone<sup>[23]</sup>. In order to overcome the challenge of *H. pylori* eradication failure, several maiden rescue regimens have recently been proposed<sup>[14,16,18]</sup>. Furthermore, Sardarian *et al*<sup>[31]</sup> compared the efficacy of a hybrid therapy (40 mg pantoprazole and 1000 mg amoxicillin for 14 d, with 500 mg clarithromycin and 500 mg tinidazole for the last 7 d, b.i.d) with sequential therapies (40 mg pantoprazole for 10 d with 1000 mg amoxicillin for the first 5 d and 500 mg clarithromycin and 500 mg tinidazole for the last 5 d, all twice daily) for *H. pylori* eradication in 396 Iranian patients<sup>[31]</sup>. The rates of compliance were 96.7% and 98.6% for the hybrid and sequential groups, respectively. The eradication rate for the hybrid group was significantly higher than that of the sequential group by both ITT (89.5% *vs* 76.7%) and PP (92.9% *vs* 79.9%) analyses. Severe side effects were observed in 2.4% of patients in the hybrid group and 3.8% of those in the sequential group.

According to the results of our study, the quintuple BOTMO regimen was successful in eradicating *H. pylori* in 86.5% and 86.7% of patients by ITT and PP analyses, respectively. Although a cure rate of > 80% was achieved, which is acceptable by the standards of Maastricht and other guidelines for successful eradication<sup>[32]</sup>, none of the regimens achieved the target threshold for an ideal eradication regimen of more than 90%. It is possible that the efficacy of the clarithromycin-based BOACT regimen used in the present study was affected by the use of clarithromycin in the failed initial eradication therapies.

In addition to being effective and compatible with regional microbial resistance patterns, a suitable anti-*H. pylori* regimen should be cost-effective, easy to administer and well-tolerated<sup>[3,18]</sup>. In the present study, approximately one-third of patients experienced adverse events, which were reported as mild to moderate. Of the total study population, only three patients discontinued treatment due to severe side effects. Generally, both treatment regimens were well-tolerated and had a good compliance (98.7% *vs* 99.04% in BOACT and BOTMO regimens, respectively).

A limitation of this study was the lack of regional estimates of eradication rates with regard to antibiotic resistance. Furthermore, the results of this study may not be applicable to patients who failed other therapies. *H. pylori* is an actively dividing spiral bacterium that assumes a coccoid morphology under stressful conditions such as antibiotic exposures<sup>[33-35]</sup>, which could contribute to treatment failures and relapse of infection<sup>[35-38]</sup>. Faghri *et al.*<sup>[35]</sup> suggested that a therapy must eradicate viable coccoids in addition to the spiral forms, in order to be successful.

In conclusion, quintuple rescue therapy using a BOTMO regimen provided higher eradication rates than the BOACT regimen. Furthermore, the drugs used in the BOTMO regimen induced fewer side effects and are widely available in regions of Iran where culturing of *H. pylori* is difficult. Thus, the BOTMO regimen could be an alternative second-line rescue therapy for Iranian patients who failed previous eradication treatment. However, the regional pattern of antimicrobial resistance necessitates that more studies in other populations be conducted. Moreover, treatment regimens of longer than seven days should also be evaluated.

## COMMENTS

### Background

*Helicobacter pylori* (*H. pylori*) infection is associated with chronic gastritis, peptic ulcer disease and gastric cancer. Therefore, the eradication of the pathogen is of great importance in order to reduce *H. pylori*-related complications. As no new drugs to treat *H. pylori* have been developed, eradication requires multiple-drug therapies. If a drug regimen fails to eradicate the bacteria, an appropriate second-line therapy should be selected.

### Research frontiers

*H. pylori* resistance to antibiotics is the most important factor in treatment failure. This necessitates the development of new, alternative protocols for successful treatment.

### Innovations and breakthroughs

This is the first study to evaluate the efficacy of two seven-day quintuple rescue

regimens including bismuth subcitrate, omeprazole and either amoxicillin, clarithromycin and tinidazole, or tetracycline, metronidazole and ofloxacin as a second-line treatment for *H. pylori* following the failure of first-line regimens in Iranian patients.

### Applications

This study indicates that quintuple therapy with bismuth subcitrate, omeprazole, tetracycline, metronidazole and ofloxacin for seven days is an effective alternative second-line rescue therapy for Iranian patients who failed first-line treatment of *H. pylori* infection.

### Terminology

Quintuple therapy for *H. pylori* eradication involves treatment with bismuth subcitrate, three antibiotics and a proton-pump inhibitor.

### Peer review

This study provides useful information and suggestions for future research evaluating treatment regimens for *H. pylori* eradication. The authors show that tetracycline-containing quintuple rescue therapy is highly effective in treating *H. pylori* eradication failures of first-line regimens in Iran.

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