

Comparison of Two Common Quadruple Therapy Protocols for Eradication of *Helicobacter Pylori* in Iran: an Open Label, Randomized, Non-inferiority, Clinical Trial

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ABSTRACT

Background:

Helicobacter pylori (*H. pylori*) is located in the digestive tract. This bacterium has a tendency to attack the stomach surface layer, mucosal changing, and eventually may involve in developing gastric cancer. In this regard, the main remaining issue is antibiotic resistance, which influences the efficacy of eradication regimens.

To assess the efficacy of two frequent anti-*H. Pylori* quadruple treatments consisting of omeprazole, bismuth, amoxicillin, and clarithromycin (OBAC) or tetracycline (OBMT).

Materials and Methods:

Patients infected with *H. pylori* were assigned to receive omeprazole 20 mg, bismuth subcitrate 240 mg, metronidazole 500 mg, and tetracycline 500 mg twice a day versus omeprazole 20 mg, clarithromycin 500 mg, amoxicillin 1000 mg, and bismuth subcitrate 240 mg twice a day. Non-inferiority analyses were conducted according to both intention-to-treat and per-protocol principles.

Results:

100 patients in each group were enrolled. The intention-to-treat eradication rate was 82% (82/100) in the group receiving OBMT and 85% (85/100) in the OBAC group. Per protocol, eradication rates were 88.1% (82/93) for the group receiving OBMT and 89.4% (85/95) for patients in the OBAC group. When considering non-inferiority analysis, there were no differences between the two groups in both methods of analysis.

Conclusion:

The eradication rate of OBMT is not inferior to OABC, and both are effective in eradicating *H. pylori* in areas with high metronidazole resistance. OBMT is a good alternative against the increasing resistance to clarithromycin.

Keywords: *H.Pylori*, Eradication , Quadruple Therapy, Tetracycline, Clarithromycin

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a bacterium found in the stomachs of over half of the world's population (1) and is the strongest known risk factor for the development of both gastric carcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. Treatment of *H. pylori* remains a challenging issue worldwide (2). Regarding the epidemiology of *H. pylori* infection in Iran, many previous studies demonstrated that its prevalence reached 90% in different parts

of the country. However, during the last decades, the prevalence may decrease due to using anti *H. pylori* treatments (3). There are many studies that illustrated that *H. pylori* strains had high resistance to metronidazole and clarithromycin in most areas due to the low eradication rate after using triple therapy. Therefore quadruple therapy, particularly in high resistance areas, is recommended (3,4).

Among different combined treatments for eradication of *H. pylori* that have been used in Iran, a type of quadruple therapy for a minimum duration of two weeks seems to be the choice of clinicians (4). A quadruple therapy consisting of omeprazole, bismuth, metronidazole, and amoxicillin was a widely used regimen in Iran. But, this regimen results in suboptimal eradication rates of *H. pylori* whilst furazolidone based quadruple regimen (OBAF) showed acceptable abilities in *H. pylori* eradication (5). The major limitation of furazolidone is that only a high-dose regimen improves the cure rate, which increases the incidence of substantial side effects (6). Using clarithromycin in place of furazolidone (OBAC) has been reported the same efficacy for both groups (7). However, along with the cost and tolerability, the resistance of clarithromycin is going to be common; therefore, in practice, we face some problems. Hence a simple, non-expensive therapeutic regimen may be required. To respond to this need, we compared the efficacy of omeprazole, bismuth, metronidazole, and tetracycline (OBMT) versus clarithromycin based previously established schedule (OBAC) for *H. pylori* eradication.

MATERIALS AND METHODS

Study design and patients

This open-label, single-center trial was conducted for the treatment of patients referred to Firoozgar Hospital, a referral university hospital in Tehran, Iran. All patients underwent pre-treatment endoscopy with biopsy for histology. Two antral biopsy samples were taken for rapid urease testing (RUT) and two for histological evaluation, which is the best method for the diagnosis of *H. pylori* infection (8,9). All procedures were done by a single expert endoscopist. Biopsy sections were reviewed by a single pathologist who was blinded to the endoscopic findings and RUT results.

Ethic

The study was in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. This study protocol was approved by the Ethics Committee of Gastrointestinal and Liver Disease Research Center, Iran University of Medical Sciences (GILDRC) number: GILDRC.IUMS.92/0420. Patients were informed about the purpose, potential side effects, and the benefits of the suggested treatments, and written informed consent was obtained from each patient.

Patients' eligibility

Eligible patients had positive *H. pylori* by rapid urease test and histological test performed on biopsy specimens (10). The exclusion criteria were as follows: age < 18 years, pregnancy, history of gastric surgery, allergy to drugs used in these regimens, gastric cancer, and impaired renal or hepatic function. Patients who used antibiotics, bismuth within 4 weeks preceding enrolment or who received previous anti *H. pylori* treatment. Patients who required systemic antimicrobial agents other than a study drug were also excluded.

Intervention and comparison

Patients were randomly assigned (1:1) using permuted randomized blocks to receive omeprazole 20 mg, tetracycline 500 mg, metronidazole 500 mg, and bismuth subcitrate 240 mg twice a day versus omeprazole 20 mg, clarithromycin 500 mg, amoxicillin 1000 mg, and bismuth subcitrate 240 mg twice a day. Patients were instructed to take bismuth and omeprazole before meals and the antibiotics with meals and at bedtime. Easier use of drugs is a major indicator of compliance; thus, we prescribed all medications twice a day. Patients were cautioned to avoid alcohol while being treated with metronidazole. They were advised to contact their physician or a central managing physician if they faced any adverse effects.

Patients were treated for a period of 14 days. We followed up with the patients at the end of the first and second week after starting the treatment for their compliance and tolerability. Absolute compliance was defined when the patients took at least 80% of the given drugs. Medications were discontinued if any intolerable adverse event occurred. Test-of-cure

Table 1: Characteristics of the patients and endoscopic findings

Variables	OBMT	OBAC	
Male/Female	33/67	50/50	
Mean age +/- SD	46.5+/-13.1	48.3+/-13.1	
Endoscopic findings	No lesion	5	3
	Gastritis	52	55
	Duodenitis	0	1
	gastroduodenitis	5	6
	GU	3	4
	DU	14	11
	GU/DU	2	3
	DU/ Gastritis	19	17

GU: Gastric ulcer; DU: Duodenal ulcer

evaluations occurred two months after the last dose of the study drugs, and all patients were asked to abstain from any antibiotics or acid-suppressing agents during this period.

Study outcomes

The primary endpoint was the *H. pylori* status, which was assessed at least 8 weeks after the end of antimicrobial therapy by repeated endoscopy with RUT and histology. Eradication was defined as no evidence of *H. pylori* infection by means of both RUT and histology.

Statistical analysis

The objective of the study was to assess whether the outcome of *H. pylori* eradication with OBMT was not inferior to OBAC. The sample size was calculated using the sample size formula for non-inferiority two proportion sample size and based on these assumptions: success rate in the control group (OBAC) = 0.85, the success rate in test drug (OBMT) = 0.81, and margin of noninferiority=0.1. This value is based on reports of other studies on *H. pylori* eradication (7, 11).

Using a one-sided α level of 0.05, we estimated that 89 patients per group were needed to demonstrate non-inferiority of OBMT with a statistical power of 80%. Expecting that up to 10% of the patients would not return for follow-up re-endoscopy, we included 200 patients in the study.

Analyses were conducted according to both

Table 2: Reported adverse events

Adverse events	OBMT	OBAC
Nausea	2	2
Vomiting	0	1
Abdominal pain	2	10
Diarrhea	1	1
Bad taste	5	7
Dry mouth	1	2
Bitter mouth	1	0
Anorexia	5	1
Headache	0	1
Skin rash	1	0
Discontinuation of treatment (n)	7	5

intention-to-treat and per-protocol principles. The non-inferiority hypothesis was assessed statistically by calculating the 95% confidence interval of risk difference.

RESULTS

The study was conducted from January 2014 to May 2016. 200 patients were enrolled; 100 patients in each group. The baseline characteristics of the patients in the two groups were comparable (Table 1). 12 patients had to discontinue their medication because of intolerable adverse events (seven and five patients in groups OBMT and OBAC, respectively). These 12 patients were not included in the per-protocol analysis. Reported adverse events are shown in Table 2. All the remaining others were compliant (took more than 80% of the given medications), and there were no cases lost to follow-up. Therefore, 188 patients completed the study and underwent follow-up endoscopy. The intention-to-treat eradication rate was 82% (82/100) in the group receiving OBMT and 85% (85/100) in the OBAC group. Per protocol eradication rates were 88.1% (82/93) for the group receiving OBMT and 89.4% (85/95) for patients in the OBAC group. When considering non-inferiority analysis, there were no differences between the two groups in both methods of analysis; details are shown in table 3.

DISCUSSION

Eradication of *H. pylori* continues to progress in the

Table 3: The eradication rate of *H. pylori* in the two groups

Analysis type	OBMT	OBAC	Rate difference (95%CI)	Interpretation
ITT (n = 200)	82/100(0.82)	85/100 (0.85)	-0.030 (-0.133-0.073)	Non-inferior
VPP (n = 188)	82/93 (0.88)	85/95 (0.89)	-0.013 (-0.103-0.077)	Non-inferior

ITT: Intention to treat analysis, PP: Per protocol analysis, OBAC: omeprazole, bismuth, amoxicillin, and clarithromycin , OBMT : omeprazole, bismuth ,metronidazole , tetracycline

last decade. In this context, many recommendations, as well as guidelines for *H. pylori* treatment, have been published. Interestingly, although triple therapy is a common treatment in some parts of the world, it is not acceptable in high prevalence zones (12,13). Hence quadruple therapy is becoming the first choice, mainly in areas with high resistance to triple therapy.

This randomized study compared two antibiotic regimens of OBMT and OBAC with demonstrated effectiveness in *H. pylori* eradication. OBMT treatment had an efficacy comparable to that of OBAC regimen on the eradication endpoint. Similar favorable response rates were observed in both treatment groups. OBMT was generally tolerated, similar to that of the comparator regimen. Patient's compliance is a key factor in bacterial eradication, as therapy for those with < 80% of adherence has a high possibility of treatment failure and later antimicrobial resistance (11,12). In the current study, fewer than 10% of the patients in any treatment group experienced adverse events, and the rates were closed in both groups (93% and 95%).

Regardless of the kind of proton pump inhibitor (PPI), antibiotic resistance in *H. pylori* strains is a worldwide challenge. Metronidazole and clarithromycin are the two most important antibiotics in the eradication of this infection. In Iran, before 2000, clarithromycin was not used widely. However, in recent years it has been used as a routine drug for *H. pylori* eradication in Iran. In this regard, Fakheri and colleagues reported the intention-to-treat and per protocol eradication rates at 85% and 90% for OBAC regimen (7).

Resistance to clarithromycin is increasing worldwide, and it is the main reason for the failure of triple therapy. In a systematic review by De Francesco and co-workers (4,14), resistance toward clarithromycin was found to be as high as 48.2-49.2% in some European countries, whilst the highest

values previously found in 2000 were 22-23.4%. In a recent meta-analysis in Iran, the pooled prevalence of clarithromycin resistance was estimated as 13% (95% CI 11-15) at the national level (16). In a study by Farzi and colleagues, it was illustrated that *H. pylori* resistance to metronidazole and clarithromycin might reach 80% and 34%, respectively, in a limited population of Iran (17). The Maastricht IV consensus conference recommends a combination of a PPI, bismuth, metronidazole, and tetracycline (OBMT) for the first-line empirical treatment in areas with clarithromycin resistance > 15-20% and as an alternative first-line treatment to standard triple therapy in areas with a low clarithromycin resistance (18).

Tetracycline is an old antibiotic. The pooled prevalence of resistance to this antibiotic is as low as 3% (95% CI 2-4) in Iran (16). Therefore, it seems to be an appropriate alternative in *H. pylori* eradication therapy. Although the prevalence of *H. pylori* resistance to metronidazole is very high (16,17), failure in treatments that consist of metronidazole can be predicted (19,20). This could be overcome by increased dosage and longer duration of treatment. In a study on 424 patients with *H. pylori* infection, including patients with metronidazole resistance, who had not received treatment before, Liang and colleagues reported an intention to treat cure rate of 87.9% and a per protocol cure rate of 93.1% using lansoprazole (30 mg twice daily) and bismuth potassium citrate (220 mg twice daily), along with 500 mg tetracycline and 400 mg metronidazole 4 times daily (LBTM) for 14 days (18). Similarly, a meta-analysis conducted by Fischbach and co-workers reported the eradication rate as more than 85% even in the presence of metronidazole resistance when treatment duration lasted 10-14 days (21). In addition, the arrival of a novel pharmaceutical composition of a 3-in-1 capsule containing bismuth subcitrate, metronidazole, and tetracycline decreased the pill count and led to better

patient compliance. Using this single-triple capsules given with omeprazole, O'Morain and others reported a 93% eradication rate by modified intention-to-treat analysis and 97% by per protocol analysis (22).

Strengths

Although 12 patients had to discontinue the treatment due to adverse events, all remaining patients had acceptable compliance. The main strength of this study was that all patients returned for their follow-up re-endoscopy.

CONCLUSION

The eradication rate of OBMT is not inferior to OABC, and both regimens are effective in eradicating *H. pylori* in areas with high metronidazole resistance. OBMT is a good alternative for the increasing clarithromycin resistance of *H. pylori*, especially in the future.

CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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