Dig Dis Sci (2009) 54:599–603
DOI 10.1007/s10620-008-0374-z

ORIGINAL ARTICLE

Efficacy of a New Therapeutic Regimen Versus Two Routinely Prescribed Treatments for Eradication of *Helicobacter Pylori*: A Randomized, Double-Blind Study of Doxycycline, Co-Amoxiclav, and Omeprazole in Iranian Patients

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Received: 22 March 2008 / Accepted: 3 June 2008 / Published online: 2 July 2008

Abstract This study compared a new regimen (group A: doxycycline, co-amoxiclav, omeprazole) and two routinely prescribed regimens (group B: amoxicillin, omeprazole, furazolidone, bismuth; group C: amoxicillin, clarithromycin, omeprazole) to find an acceptable first-line treatment option for *Helicobacter pylori*. The study population consisted of 189 patients who referred to our clinic to undergo endoscopy due to ulcer-like dyspepsia. The *H. pylori* eradication rate was 68% in group A, 56% in group B, and 70% in group C according to per-control analysis. There was no statistically significant difference in *H. pylori* eradication between groups A and B ($P = 0.187$), groups A and C ($P = 0.857$), and groups B and C ($P = 0.15$). In conclusion, although none of the three eradication regimens can be recommended as a first-line eradication treatment, the new regimen is at least as effective and probably better tolerated than the two routinely applied regimens.

Keywords *Helicobacter pylori* · Doxycycline · Co-amoxiclav · Omeprazole

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Introduction

Helicobacter pylori is a gram-negative, noninvasive, non-spore-forming, spiral-shaped bacteria that is responsible for one of the most prevalent chronic infections worldwide [1]. It has established to be one of the main risk factors for developing peptic ulcer and is also associated with chronic active gastritis, gastric adenocarcinoma, and type B low-grade mucosa-associated lymphoma [2–4]. Although still controversial, some recent studies showed the role for *H. pylori* in the pathogenesis of nongastric pathologies such as coronary artery disease, insulin resistance, and some autoimmune disease [5].

The incidence rate of *H. pylori* infection in the developed countries may be as low as 30%, whereas in developing and underdeveloped countries, it is more than 80%; in Iran, this rate is 86% [6]. Clustering of the organism in families [7] suggests person-to-person transmission, a common environmental source, and a genetic basis for differences in susceptibility to the infection [8]. Childhood is thought to be the primary period of risk for *H. pylori* acquisition [9].

Twenty years after the discovery of *H. pylori*, although no simple eradication regimen has been proposed, several regimens are considered to be satisfactory. Treatment failures are, however, not uncommon and are not equally prevalent in different countries, and the study of their possible causes has not been performed on a large scale [10]. Antibiotic resistance is the first factor to be considered and indeed seems to be a real cause of failure, especially for clarithromycin-based therapies [11]. Other factors, such as patient characteristics, underlying disease, and environmental factors, have rarely been explored in a large group of patients. Antibiotic resistance, poor compliance, and intolerance to therapeutic regimens are said to

be the major problems with eradication of *H. pylori* [12]. In recent years, resistance to antibiotic therapy has increased, and multiple drug therapies have decreased patient compliance.

In a recent in vitro study performed in our center, the overall *H. pylori* resistance rates were 72.6% to metronidazole, 9.4% to clarithromycin and furazolidone, 20.8% to amoxicillin, and 4.7% to tetracycline and ciprofloxacin, whereas *H. pylori* isolated from patients with peptic ulcer disease and dyspepsia were not resistant to co-amoxiclav. This study showed that the considerable rate of resistance to amoxicillin alone virtually disappears after addition of clavulunate [13].

Clarithromycin-based triple therapy is used widely worldwide and is also supported by the Maastricht 2–2000 Consensus Report [14]. Triple therapy including clarithromycin resulted in an acceptable eradication rate, whereas when the combination of amoxicillin, clarithromycin, and omeprazole was used for 7 and 14 days, *H. pylori* eradication rates were about 86% and intent-to-treat eradication rates were 73.1% and 65%, respectively [15].This regimen also has a high cost due primarily to the price of clarithromycin.

Quadruple therapy using a furazolidone-based regimen is also commonly used in our country, and although it is relatively inexpensive, it seems not to be as effective as early studies showed. In a recent report, standard quadruple therapy consisting metronidazole, bismuth, tetracycline, and omeprazole was said to be superior to quadruple therapy with furazolidone, tetracycline, bismuth, and levofloxacin-based triple therapy consisting ciprofloxacin bismuth subcitrate [16]. It also suffers from a high rate of intolerance primarily due to furazolidone and drug and food interactions.

In this study, we aimed to compare two routinely prescribed regimens (amoxicilin, omeprazole, furazolidone, bismuth/amoxicillin, clarithromycin, omeprazole) and a new regimen (doxycycline, co-amoxiclav, omeprazole) to attempt to find an acceptable first-line treatment option for *H. pylori* in our geographic area.

Methods

Determination of *H. pylori* Status

H. pylori infection was diagnosed from biopsy samples routinely taken by endoscopy from patients referred to our clinic for ulcer-like dyspepsia. Four biopsies, three from the antrum for histology, were taken at each endoscopy. An additional antral biopsy was taken for the CLO test (rapid urease test). Formalin-fixed, paraffin-embedded tissue sections were stained separately with hematoxylin and eosin for the evaluation of gastritis and with Warthin-Starry stain to detect *H. pylori*. All histology preparations were evaluated by a pathologist who was blinded to the patients' clinical status, treatment, and the results of other tests. Infection by *H. pylori* was defined as positivity of histology and CLO test.

Exclusion Criteria

Patients affected by serious concomitant illnesses (hepatic, cardiorespiratory, or renal diseases; insulin-dependent diabetes mellitus; neoplastic diseases; or coagulopathy) and those with previous exposure (up to 4 weeks before the first eradication attempt) to drugs capable of interfering with the susceptibility test, such as proton pump inhibitors (PPI) or antibiotics, were excluded. Patients younger than 18 years, patients with previous gastric surgery, and patients with allergy to any of the drugs used in the study were also excluded.

Patients

From patients who were *H. pylori* positive, 189 individuals participated in the study and provided written informed consent. One hundred and seventy (89.9%) (74 men and 96 women) of patients completed the study. Patients were randomly divided into three groups with different therapeutic regimens. Group A included 67 patients treated with the new therapeutic regimen containing doxycycline 100 mg b.i.d, co-amoxiclav 625 mg t.i.d, and omeprazole 20 mg b.i.d. In this group, 60 (25 men and 35 women) patients completed the study. Group B included 69 patients treated with amoxicillin 1 g b.i.d, omeprazole 20 mg b.i.d, furazolidone 100 mg b.i.d, and bismuth 240 mg b.i.d. Sixty patients (26 men and 34 women) remained till the end of the study in this group. Group C included 53 patients treated with amoxicillin 1 g b.i.d, clarithromycin 500 mg b.i.d, and omeprazole 20 mg b.i.d. Fifty (23 men and 27 women) of patients completed the study (Table 1). All three groups were treated with these therapeutic agents for 2 weeks.

All the patients underwent urea breath test (UBT) with 13C (13C-UBT) 4–6 weeks after treatment. All study medication was matched with placebo to maintain the double-blind nature of the study. Patients were instructed to avoid antiulcer or ulcerogenic medication and any antibiotic other than the study drug from study enrollment through the end of the posttreatment period.

Eradication of *H. pylori*

H. pylori eradication was defined as a negative result in 13C-UBT performed at least 4 weeks after the end of treatment.

Table 1 Treatment groups to which patients were randomized

Group A	Doxycycline 100 mg b.d.
	Co-amoxiclav 625 mg T.D
	Omeprazole 20 mg b.d.
Group B	Amoxicilin 1 g b.d.
	Omeprazole 20 mg b.d.
	Furazolidone 100 mg b.d.
	Bismuth 240 mg b.d.
Group C	Amoxicilin 1 g b.i.d,
	Clarithromycin 500 mg b.i.d
	Omeprazole 20 mg b.i.d. 50

Statistical Analysis

A per-protocol analysis was conducted for each efficacy endpoint. A more conservative (worst case), intention-to-treat analysis, which included patients with missing data as well as those unable to complete the regimens as failures, was also conducted for *H. pylori* eradication. The comparability of the treatment groups was assessed with respect to demographic variables and medical and social histories by the χ^2 test and one-way analysis of variance.

Ethics and Consent

The study was approved by local Ethics Committees. Each patient gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki as revised by the 41st World Medical Assembly, Hong Kong, September 1989.

Results

One hundred eighty-nine (189) patients were enrolled in the study based on positive CLO test and histology results and randomized to receive therapeutic regimen. *H. pylori* was eradicated from 41 of 60 (68%) patients in the doxycycline b.i.d., co-amoxiclav t.i.d., and omeprazole b.i.d. group (group A), 34 of 60 (56%) in the amoxicillin b.i.d., omeprazole b.i.d, furazolidone b.i.d., and bismuth b.i.d. group (group B), and 35 from 50 (70%) in the amoxicillin b.i.d., clarithromycin b.i.d., and omeprazole b.i.d. group (group C) according to per-control analysis (Table 2). There was no statistically significant difference in *H. pylori* eradication between groups A and B ($P = 0.187$), groups A and C ($P = 0.857$), and groups B and C ($P = 0.15$).

By a worst-case intention-to-treat analysis, in which patients who failed to return for the follow-up evaluation were considered to have persistent *H. pylori* infection, the *H. pylori* eradication rates were 61% (41 of 67) in group A, 49% (34 of 69) in group B, and 66% (35 of 53) in group C (Table 2). There was no statistically significant difference in *H. pylori* eradication between groups A and B ($P = 0.162$), groups A and C ($P = 0.585$), and groups B and C ($P = 0.064$).

Table 2 *Helicobacter pylori* eradication rate in three groups

	Eradication rate	
	Per-protocol (PP) analysis	Intention-to-treat (ITT) analysis
Group A	41 of 60 (68%)	41 of 67 (61%)
Group B	34 of 60 (56%)	34 of 69 (49%)
Group C	35 of 50 (70%)	35 of 53 (66%)

Discussion

Despite the publication of numerous *H. pylori* eradication trials, confusion persists concerning the relative efficacy and tolerability of several regimens. Much of the uncertainty originates from the fact that comparisons often have been based on results from separate trials that have used different methods. Shortcomings in trials have also limited the opportunity to compare efficacy and safety results across trials and even within them. The limitations include insufficient power to detect significant differences, failure to include intention-to-treat analyses, failure to employ the most sensitive methods for detecting *H. pylori*, evaluation of eradication only in patients with healed ulcers, and failure to determine antibiotic susceptibility and measure compliance [17].

Use of triple antibiotic therapy is regarded as a gold standard in *H. pylori* eradication and has been so verified in various reports. Patient assurance and safety, and cost-effectiveness including noninvasive *H. pylori* testing and eradication, were validated once again in a recently reported randomized trial with a 1-year follow-up [18]. According to the Maastricht 2–2000 Consensus Report, first-line *H. pylori* eradication therapy should be a 7-day triple therapy using a PPI or ranitidine bismuth citrate (RBC) combined with clarithromycin and amoxicillin or metronidazole [14]. Modification of certain aspects of eradication guidelines may be justified at the specialist level, as they help identify the potential factors determining therapy outcome.

Selection of first-line eradication therapy is important in the cost-effective approach to dyspepsia management and also in avoiding primary failure [19, 20]. Some recent work has focused on this aspect of eradication therapy [21–25] and compared various available eradication regimens.

Although the new regimen that includes clavulanate showed great promise during in vitro trials, it was not as

effective when applied in vivo. This phenomenon, although somewhat disappointing, is not unknown in *H. pylori* eradication and further emphasizes the need for in vivo testing of all *H. pylori* eradication regimens. The clarithromycin-based regimen also had a disappointingly low eradication rate compared with studies in other areas (70% vs 94%) [26], and when considered along with its higher price, it cannot be recommended as an acceptable first-line eradication regimen.

It also should be mentioned that some host factors—most notably the underlying pathology or disease state—may also be involved in the overall low eradication rate observed in this study. A significant majority of our study population (90%) were cases of nonulcer dyspepsia, which is known to have a lower rate of response to *H. pylori* eradication compared with gastric or duodenal ulcers [27].

In conclusion, although none of the above three eradication regimens can be recommended as a first-line eradication treatment for our region, the new eradication regimen is at least as effective and probably better tolerated than the two routinely applied regimens, and its routine use can be justified while waiting for highly needed further studies on new drug combinations.

Acknowledgment The authors thank personnel of the endoscopy ward of Nemazee hospital for their kind efforts in performing this study. We also thank the Gastroenterology Research Center of Shiraz University of Medical Science for supporting this study.

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