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RAPID COMMUNICATION

Omeprazole-based triple therapy with low-versus high-dose of clarithromycin plus amoxicillin for *H pylori* eradication in Iranian population

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Abstract

AIM: To investigate the efficacy and tolerability of *H pylori* eradication in an omeprazole-based triple therapy with high- and low-dose of clarithromycin and amoxicillin.

METHODS: One hundred and sixty *H pylori* positive patients were randomly assigned to two groups based on the following 2 wk investigation; (1) group A or low-dose regimen received omeprazole 20 mg b.i.d, clarithromycin 250 mg b.i.d and amoxicillin 500 mg b.i.d; and (2) group B or high-dose regimen received omeprazole 20 mg b.i.d, clarithromycin 500 mg b.i.d and amoxicillin 1000 mg b.i.d. During the study *H pylori* status was assessed by histology and rapid urease test prior and by ^{13}C-urea breath test 6 wk after the therapy. Standard questionnaires were administered to determine the compliance to treatment and possible adverse events of therapy. Data were subject to χ^2 to compare the eradication rates in the two groups. The significant level of 95% ($P \leqslant 0.05$) was considered statistically different.

RESULTS: We found that the per-protocol eradication rate was 88% (68/77) in group A, and 89% (67/75) in group B. The intension-to-treat eradication rate was 85% (68/80) in group A and 83.75% (67/80) in group B. Overall adverse events were 26% in group A and 31% in group B. The adverse events were generally mild in nature and tolerated well in both groups with a compliance of 98% in group A *vs* 96% in group B.

CONCLUSION: The omeprazole-based low dose regimen of clarithromycin and amoxicillin for two weeks in *H pylori* eradication is as effective as high dose regimen in Iranian population.

INTRODUCTION

H pylori is associated with chronic active gastritis, peptic ulcer diseases, gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma[1-3]. Numerous treatment regimens for *H pylori* eradication with particular attention to duration and dosage have been adopted in various geographic regions of world with contradictory results[4-6]. The goal of all these attempts is to obtain a cheap, safe, tolerable and acceptable *H pylori* eradication rate regimen. An *H pylori* regimen should achieve at least an 80% eradication rate[7,8]. Classical triple therapy based on H2-receptor antagonist or a proton pump inhibitor (PPI) due to high prevalence (75.2%) of *H pylori* resistance to metronidazole in Iran, is not accompanied by acceptable eradication rates[9,10]. In a randomized study of two weeks treatment in Iranian duodenal ulcer patients with bismuth triple therapy (bismuth, metronidazole and amoxicillin), the cure rate for *H pylori* was 46.0% by per-protocol (PP) analyses[11]. Furazolidone, a cheap antibiotic, has been focus of attention as a substitute for clarithromycin or metronidazole in few clinical trials of bismuth triple and quadruple therapy in Iran[12,13]. In a bismuth quadruple therapy with two different doses of furazolidone, intention-to-treat (ITT) and PP eradication rates were 72% with low and 92% with high dose of furazolidone respectively[13]. Regardless of this study, in practice its higher doses are accompanied by poor compliance and severe side-effects, and so far no Hp consensus group has recommended its routine use. To keep in mind these facts and overcome the above shortcomings, the first line of therapy as suggested by European, American, and Asian-Pacific guidelines for *H pylori* eradication that combines a PPI with clarithromycin and either amoxicillin

or metronidazole should be considered as first line of *H pylori* treatment in Iranian patients. Based on high resistance of *H pylori* strains to metronidazole in Iran, non-metronidazole containing regimens are recommended for *H pylori* eradication in our country. Since short-term regimens are not effective in *H pylori* eradication in Iranian patients, a 10-14 d therapy is needed[14]. As this regimen is costly for routine use in developing countries, dose reduction is an option to decrease its cost. There are limited studies that have evaluated the efficacy of both clarithromycin and amoxicillin in low-dose regimens in *H pylori* eradication with a PPI-based triple therapy[15-19]. Therefore, we tried to investigate the efficacy and tolerability of omeprazole-based triple therapy with high and low doses of clarithromycin and amoxicillin in *H pylori* eradication in Iranian population.

MATERIALS AND METHODS

Between October 2004 and September 2005, 160 consecutive *H pylori*-infected patients, 18-80 years of age, were recruited for this study. The patients were excluded from enrolment if they had taken proton pump inhibitors, bismuth preparations or antibiotics within 4 wk prior to the study; had histories of gastric or duodenal surgery, allergy to medications or endoscopic evidence of gastric malignancy, gastric outlet obstruction, bleeding or if they had clinically significant cardiovascular, hepatic, pulmonary metabolic or psychiatric diseases. The *H pylori* infection was defined as positive when both rapid urease test and histology were positive for *H pylori* documentation. In the biopsy rapid test, two biopsy specimens (one from antrum and one from corpus on the greater curvature) were examined. Four biopsy specimens (two from antrum and two from the mid-corpus on the greater and lesser curvature) underwent histopathological assessment. Eligible patients were randomized to receive the two following regimens: group A or low-dose regimen (n = 80) received omeprazole 20 mg b.i.d, clarithromycin 250 mg b.i.d and amoxicillin 500 mg b.i.d, and group B or high-dose regimen (n = 80) received omeprazole 20 mg b.i.d, clarithromycin 500 mg b.i.d and amoxicillin 1000 mg b.i.d for two weeks. Eradication was confirmed by ^{13}C-urea breath test 6 wk after completion of treatment. Results under 5 cut-off were considered negative. Adverse events were prospectively evaluated. They were assessed as mild (discomfort not interfering with daily activity); moderate (discomfort interfering with daily activity); and severe (discomfort resulting in discontinuation of therapy). Compliance was checked by pill count at the end of treatment. Poor compliance was defined as taking less than 70% of pills. Eradication rates were evaluated by ITT and PP analyses. The eradication and adverse event rates in the two treatment groups were compared using χ^2 test. A P value less than 0.05 was considered statistically significant. Data were analyzed using the SPSS for Windows (version 11.5; SPSS, Inc, Chicago, Illinois, USA).

RESULTS

Demographic and outcome data of two eradication regimen groups are summarized in Table 1. No significant difference was found between the two groups of patients with regard to clinical variables. Five patients (2 in group A and 3 in group B) with poor compliance and 3 (1 in group A and 2 in group B) with incomplete follow-up therapy were excluded from PP analysis for *H pylori* eradication. The per-protocol eradication rate was 88% in group A, and 89% in group B. The ITT eradication rate was 85% in group A and 83.75% in group B. The differences were not statistically significant between the two groups by ITT and PP. All the patients receiving at least one dose of medications were included in adverse event analysis, and 26% of the group A and 31% of group B reported at least one adverse event during the therapy. Diarrhea was the most common adverse event in both groups (5% in group A *vs* 9% in group B). All but 5 (2 in group A and 3 in group B) complied with the eradication therapies and took more than 70% of assigned tablets. Both groups displayed similar compliance rates (98% in group A *vs* 96% in group B).

Table 1 Demographic data and outcomes of two enrolled groups

Data	Group A (n = 80)	Group B (n = 80)
Mean age (yr) (mean ± SD)	52.4 ± 13	53.1 ± 12.3
Gender (male/female)	55/25	57/23
Eradication rate		
Intension-to-treat	85% (68/80)	83.75% (67/80)
Per-protocol	88% (68/77)	89% (67/75)
Adverse events		
Mild	20% (15)	22% (17)
Moderate	5% (5)	8% (6)
Severe	1.25% (1)	2.5% (2)
Compliance	98% (78/80)	96% (77/80)

DISCUSSION

The results of this study confirm that efficacy of low and high dose regimens of clarithromycin and amoxicillin and comparable omeprazole dose (20 mg b.i.d) are equal in *H pylori* eradication in Iranian population. The treatments were well tolerated and associated with a high compliance rate. Many studies have compared different doses of clarithromycin in *H pylori* eradication, with contradictory results, but those that have evaluated clarithromycin-amoxicillin combination in low-dose regimens for *H pylori* eradication are scarce[15]. Hp consensus groups have generally recommended a 500 mg b.i.d dosage of clarithromycin for *H pylori* eradication[7,8]. However, some issues with regard to the clarithromycin dosage need to be addressed. MACHI study produced disappointing results for low-dose clarithromycin regimens, with an eradication rate of 79.5% by intension-to-treat analysis compared with 90.6% for the clarithromycin 500 mg b.i.d regimen[16]. A meta-analysis also showed that pooled eradication rate of the clarithromycin 500 mg b.i.d regimen was 86.6% by ITT analysis and 89.5% by PP analysis, which were significantly higher than those achieved with the clarithromycin 250 mg b.i.d regimen, 78.2% by ITT and 83.3% by PP analyses[19]. However, even in that meta-analysis, subgroup analysis

showed that proton pump inhibitor dosing frequency affected the efficacy of *H pylori* eradication. On the basis of proton pump inhibitor b.i.d regimens, the *H pylori* eradication rates by pooled PP analysis were 86.1% and 89.6% in the clarithromycin 250mg b.i.d and 500 mg b.i.d regimens, respectively. In contrast, a recent Japanese study showed that clarithromycin 200 mg b.i.d regimen was as effective as 400 mg b.i.d[18]. In addition, a multi-center study performed in France demonstrated a somewhat higher, although not significant, eradication rate with low-dose clarithromycin triple therapy compared with the conventional regimen[17]. In a study by Miwa H *et al*[15]using different doses of omeprazole-clarithromycin-amoxicillin, in their low-dose group of omeprazole 20 mg, amoxicillin 750 mg and clarithromycin 200 mg all b.i.d, the eradication rates by ITT and PP were 82.5% and 90% respectively. In our study, the eradication rate of low-dose regimen was 85% and 88% by ITT and PP analysis, respectively. Because of the high metronidazole resistance in our country (75.2%)[10] and low eradication rate of *H pylori* with metronidazole containing regimens and shortcomings with other applied *H pylori* eradication regimens in Iran, the first line of *H pylori* treatment as suggested by most *H pylori* consensus groups, the PPI-based therapy with low-dose regimen of clarithromycin-amoxicillin seems to be a good option to overcome its high cost in developing countries. In a study by Malekzadeh *et al*[14] using a 7-d conventional therapy with clarithromycin, regardless of low prevalence of *H pylori* resistance to clarithromycin in their report (1.2%), the eradication rate was unacceptably low (35.5% in ITT). This low eradication rate has been attributed to the high prevalence of cancer in the areas of the study, their conclusion was that patients in this high-prevalence cancer area may have a higher bacterial load in gastric mucosa with different biological behaviors, Cag A strains or host-immune response. It has been estimated that the rate of eradication increased by 9% by extending duration of therapy from 7 to 10 d[20]. Based on these reports and our results, efficacy of proton pump triple therapy with conventional and low-dose regimens of clarithromycin and amoxicillin with 7, 10 and 14 d requires more evaluation in different geographic regions of Iran by further multi-center head-to-head comparison studies in our country. In conclusion, two weeks triple therapy with a proton pump inhibitor and low-dose regimen of clarithromycin and amoxicillin is as effective as high-dose regimen, and has acceptable eradication rate and the best cost-benefit ratio in Iranian population.

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