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ORIGINAL ARTICLE

Quadruple of Bismuth, Pantoprazole, Amoxicillin, and Metronidazole for the First-Line *Helicobacter pylori* Eradication Therapy

Birinci Basamak Helicobacter pylori Eradikasyon Tedavisinde Dörtlü Bizmut, Pantoprazol, Amoksisilin ve Metronidazol Kullanımı

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Abstract

Introduction: To determine the *Helicobacter pylori* (*H. pylori*) eradication rates with a quadruple treatment regimen consisted of pantoprazole, bismuth subcitrate, metronidazole, and amoxicillin for 14 days in a country with high metronidazole and clarithromycin resistance rates.

Methods: All patients were prescribed 14-day quadruple therapy (pantoprazole 40 mg twice daily, bismuth subcitrate 600 mg 2 × 1, amoxicillin 1 g twice daily, and Metronidazole 500 mg three times a day, for 14 days). The success rates of eradication treatment were investigated with stool *H. pylori* antigen test performed 2 months after eradication.

Results: Among 132 *H. pylori* -infected treatment-naive patients, 8 (6.0%) patients could not complete the study due to adverse events or lost from the follow up. Among 124 patients who completed the study, 10 patients presented with a positive result on stool *H. pylori* antigen testing at 8th week, while in remaining 114 cases, the test result was negative. In intention to treat analysis, the eradication rate was determined as 86.4% (95% confidence interval [CI]=81.2%–92.3%), while in per-protocol analysis, the eradication rate was 91.9% (95% CI=88.2%–96.1%).

Discussion and Conclusion: With low adverse events and high compliance rates, this treatment modality should be kept in mind for *H. pylori* eradication especially in regions with high clarithromycin resistance.

Keywords: Amoxicillin; Bismuth subcitrate; *Helicobacter pylori* eradication; Metronidazole

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The role of *Helicobacter pylori* (*H. pylori*) infection in chronic gastritis, peptic ulcers, gastric atrophy, and gastric malignancy has been determined clearly and so that *H. pylori* eradication is strongly advised in treatment.[1] Nevertheless, with the rising rates of antibiotic resistance, especially for the clarithromycin, *H. pylori* eradication rates were reported to be less than 80% even with 14 days of standard conventional triple therapy consisted of PPI, amoxicillin, and clarithromycin.[2]

The differences in the prevalence of antibiotic resistance are one of the most important determinants of the dissimilar efficacy rates of treatment regimens in different regions of the world. In a recent study from our country, the rates of resistance to different antibiotics among *H. pylori* strains were evaluated, and researchers reported that all strains were susceptible to amoxicillin and tetracycline, while clarithromycin, metronidazole, and levofloxacin resistance rates were 36.7%, 35.5%, and 29.5%, respectively; additionally, multiple resistances were reported in 19.3% of the isolates.[3] Moreover, other than the resistance, adherence to the treatment and tolerating side effects of the drugs is another big problem. The compliance was reported as low as 79.2% in tetracycline containing quadruple therapies.[4]

The aim of this study was to establish the H. pylori eradication rates with a quadruple treatment regimen consisted of pantoprazole, bismuth Subcitrate (BS), metronidazole (MET), and amoxicillin (AMO) for 14 days.

Materials and Methods

Patients

A total of 132 *H. pylori*-infected naive adult patients, diagnosed with endoscopic biopsies, were included in the study. Among participants, 43 were male, while 89 were female. All patients were prescribed 14-day quadruple therapy (pantoprazole 40 mg twice daily, BS 600 mg 2 × 1, amoxicillin 1 g twice daily, and metronidazole 500 mg three times a day).

Patients treated with antibiotics, PPI, or bismuth compounds within the preceding 30 days, patients treated for *H. pylori* infection before, with Zollinger–Ellison syndrome, with allergy to any medications in the study, pregnant or lactating patients, and patients taking nonsteroidal antiinflammatory drugs were excluded.

Outcomes and Follow Up

The primary endpoint was the successful eradication of H. pylori. The H. pylori eradication failure was defined as positive results for the H. pylori antigen in stool (ABON biopharma, Hangzhou, China) 8 weeks after the end of the treatment. All patients were controlled at the end of 2nd week to assess drug compliance and adverse effects of the medications.

Drug compliance was evaluated in all patients. Failure to complete 80% of all medications due to adverse effects was defined as poor compliance.[5,6] All adverse events including abdominal discomfort, dizziness, nausea, vomiting, headache, taste perversion, diarrhea, and skin rash were asked.

Table 1. Demographic features of study participants and the results of treatment

Characteristics	
Age (years)	36.76±9.42 (range: 22–57)
Gender (female/male)	89/43
Smoking n, %	46 (34.8%)
Intention to treat eradication rate	114/132 (86.4%)
Per-protocol eradication rate	114/124 (91.9%)
Adverse events	21/132 (15.9%)
Compliance	124/132 (93.9%)

Statistical Analysis

The eradication rate, presence of adverse events, and level of patient compliance were the primary outcome variables. Intention to treat (ITT) and per-protocol (PP) analysis were performed to determine eradication rates using the SPSS program (Statistical Package for the Social Sciences version 21, Chicago, IL, USA). ITT analysis included all patients who received at least one dose of the study medication. In PP analysis, patients that could not complete the treatment for any reason or were lost to follow up were not included. A p value <0.05 was considered as statistically significant.

Results

Among 132 patients, 8 (6.0%) patients could not complete the study due to adverse events or lost from the follow up. Demographic features of the study participants are summarized in Table 1.

Among 124 patients who completed the study, 10 patients presented with a positive result on stool *H. pylori* antigen testing at 8th week, while in the remaining 114 cases, the test result was negative. In ITT analysis, the eradication rate was determined as 86.4% (95% confidence interval [CI]=81.2%–92.3%), while in PP analysis, the eradication rate was 91.9% (95% CI=88.2%–96.1%) (Table 1). When the patients were grouped regarding their genders, no significant difference was found in PP eradication rates (p=0.41),

but when the patients were grouped according to their smoking status, in smokers, the PP eradication rates were statistically significantly lower (84.7% versus 96.1%; p=0.04) compared with the nonsmokers.

In 21 of all 132 patients, some degrees of adverse events were reported. Among those 21 patients, 5 (3 female, 2 male) left the study due to those adverse events (mainly abdominal pain and dizziness). Conversely, among 124 patients who completed the study, 16 (11 female, 5 male) of them reported to exhibit adverse drug events including dizziness, headache, and gastrointestinal symptoms, which were commonly mild and especially reported in the first few days of the treatment. Interestingly, after treatment, all those 16 patients presented with negative results in stool antigen test on the 8th week. Only five patients left the study due to adverse events and the drug compliance rate was (96.2%).

Discussion

In this study, we assessed the *H. pylori* eradication rates with a quadruple treatment regimen consisted of pantoprazole, bismuth citrate, metronidazole, and amoxicillin for 14 days, and we determined satisfactory results for eradication. The adverse events reported were low, and the compliance rate was high in this treatment modality. Though metronidazole resistance was not low in our region, researchers reported that with at least 10 days of full dose therapy, this resistance can be overwhelmed, which is not the condition for clarithromycin resistance.[7,8] Moreover, due to the greater tolerability of metronidazole compared with tetracycline in our clinical observations, we chose this treatment modality and aimed to define its success rates in *H. pylori* eradication.

Amoxicillin works by prying with the peptidoglycan synthesis, while metronidazole produces oxygen-free radicals and damages the DNA-helicoidal structure of bacteria.[9,10] With very low, almost absent resistance rates, amoxicillin has been one of the main antibiotics used in *H. pylori* therapy. Conversely, metronidazole resistance has been determined in high levels in different countries.

H. pylori infection is very common in all over the world, but unfortunately, a consensus still does not exist on the regimens for *H. pylori* eradication.[9] Many studies exist in literature about the *H. pylori* eradication treatment regimens. With the increasing resistance rates, new treatment modalities are required since treatment modalities advised by the international committees also do not provide same eradication rates in different parts of the world. Similar with our study, Zhang et al.[11] evaluated the efficacy and tolerability of replacing tetracycline with amoxicillin in bismuth quadruple therapy, and they reported 94.9% eradication rate by PP analysis and 88.9% eradication rate by ITT analysis in metronidazole group. The authors suggested that amoxicillin containing modified 14-day bismuth quadruple therapy may be regarded as the first-line treatment. In another place of the world, Vilaichone et al.[12] reported that 7 days of amoxicillin containing modified 14 day bismuth quadruple therapy was highly effective (90.1%) for metronidazole-sensitive *H. pylori* infections; however, the efficacy declined with metronidazole resistance (72.7%). The authors suggested that longer duration of this regimen might be required to improve the eradication rate.

Regional differences especially in resistance rates are very important in determining the *H. pylori* eradication rates. With a first-line bismuth-containing 5-day concomitant quintuple therapy, Dolapcioglu et al.[13] reported high (97.2%) compliances as well as high eradication rates with ITT (93.1%) and PP (95.7%) analysis. With the increasing clarithromycin resistance rates in our country, treatments without clarithromycin are also studied. Gungor et al.[14] compared the efficacy and tolerability of five different regimens for *H. pylori* eradication, and they reported that in regimens without bismuth, the eradication rates with ITT and PP analysis were very low (less than 50%). However, in that study, the eradication rates in bismuth-containing therapy groups were also not satisfactory (between 60% and 80%, approximately). Ergül et al.[15] reported 90.7% of eradication rate with 14-day bismuth-lansoprazole-amoxicillin-clarithromycin regimen for *H. pylori* eradication as a first-line therapy. However lower eradication rates with those treatment regimens were also reported, in our country. Next, Kadayifci et al.[16] compared the efficacy of bismuth-based quadruple (bismuth subsalicylate, esomeprazole, tetracycline, and amoxicillin) and concomitant (esomeprazole, tetracycline, amoxicillin and metronidazole) regimens, and they reported that ITT and PP eradication rates were 79% and 89.7% in the bismuth group and 74% and 80.4% in the concomitant group. Toros et al.[17] evaluated the success rates of lansoprazole, amoxicillin and clarithromycin plus metronidazole treatment for 14 days in *H. pylori* eradication and reported total eradication rate of 75%. So, in countries like Turkey, with high antibiotic resistance rates, new treatment regimens for *H. pylori* eradication are required. At least 1,500 mg daily dose for at least 10 days has been suggested in previous studies to overcome the resistance and for that reason; we prescribed 3 × 500 mg metronidazol for 14 days in that study.[18]

Smoking was described as a reason for treatment failure in *H. pylori* eradication in previous studies.[19,20] Our results were also supporting these data with lower eradication rates in smokers compared with nonsmokers, but the PP eradication rate was still higher than 80% (84.7%) in smokers.

There are some limitations of this study that should be mentioned. First, studying antibiotic resistance rates and giving the eradication rates on the basis of resistance may be more appropriate but expensive. Second, we evaluated the eradication rates with stool antigen instead of C14 urea-breath test which may also be regarded as a limitation. However, again 14 days of proton-pump-inhibitor free period was awaited before testing, and a negative stool test after treatment was determined as adequately predicting the cure of the infection, previously.[21] Another limitation of the study is the following: although age was also defined as a factor affecting the eradication rates,[22,23] we did not group or compare the patients regarding their ages.

In conclusion, in this study, we reported the first-line eradication rates with a quadruple treatment regimen that is consisted of pantoprazole, BS, metronidazole, and amoxicillin for 14 days, and we determined satisfactory eradication rates in Turkey where the clarithromycin and metronidazole resistance rates were approximately higher than 35%. With low adverse events and high compliance rates, this treatment modality should be kept in mind for the H. pylori eradication especially in regions with high clarithromycin resistance. Larger studies are necessary especially in countries with high metronidazole resistance rates, as our country, to confirm our results and to define this treatment as one of the first-line empiric treatment modalities.

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Conflict of Interest: None declared.

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