

# Efficacy of Bismuth-Containing Quadruple Therapy as First-line Treatment for *Helicobacter pylori* Infection

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## ABSTRACT

**Background and aim:** *Helicobacter pylori* (*H. pylori*) infection can cause chronic gastritis, peptic ulcer disease, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. For this reason, eradication of *H. pylori* has become an important issue. In recent years, failure of eradication therapy with standard eradication regimes had directed toward new therapeutic alternatives. The present study aimed to show the efficacy of bismuth-containing quadruple regimen for the first-line treatment of *H. pylori* infection.

**Materials and methods:** *H. pylori* positive patients received a quadruple therapy consisted of esomeprazole 20 mg bid, colloidal bismuth subcitrate 600 mg bid, tetracycline 500 mg qid and metronidazole 500 mg tid for 7 days. The diagnosis of *H. pylori* infection was performed by the histopathological assessment of gastric biopsies. Six weeks after completion of therapy, *H. pylori* status was rechecked by C14 urea-breath test.

**Results:** A total of 115 patients have completed the protocols (upper gastrointestinal endoscopy, treatment, urea-breath test). *H. pylori* eradication rate was found to be 87%. This eradication rate is significantly higher than those of classic triple therapies in the literature.

**Conclusion:** The bismuth-containing quadruple regimen achieved an acceptable and very higher eradication rate than those of classic triple therapies in the literature. It can recommend as a first-line therapy for *Helicobacter pylori* infection.

**Abbreviations:** HP: *Helicobacter pylori*; MALT: Mucosa-associated lymphoid tissue lymphoma; PPI: Proton pump inhibitor; CPM: Count per minute; SD: Standard deviation.

**Keywords:** *Helicobacter pylori*, First-line therapy, Bismuth, quadruple regimen.

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## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) infection is one of the most common human infections, and about half of the world's population carries this bacterium.<sup>1</sup> The eradication of *H. pylori* from gastric mucosa is an important issue because of an importance in the development of peptic ulcer, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma.

The third Maastricht Meeting, a drug regimen of a combination of the proton pump inhibitor (PPI), clarithromycin, amoxicillin or a nitroimidazol derivative (metronidazole or tinidazol) containing triple combinations, or PPI plus bismuth citrate plus metronidazole plus tetracycline as a quadruple eradication therapy has been proposed for first-line therapy.<sup>2</sup> Clarithromycin-based triple therapies have been widely preferred in both Turkey and World. The eradication rates were over 90% in early years after starting of eradication therapy,<sup>3</sup> but the rate decreased from 40 to 50% in recent years.<sup>4,5</sup> This decline is attributed to clarithromycin resistance. Currently, high rate of clarithromycin ( $\geq 20\%$ ) resistance rates have been observed in developed countries of Europe and Asia and in Turkey.<sup>6,7</sup>

The failure of eradication therapy with standard eradication regimes had opened a new spectrums of therapeutic alternatives. The present study aimed to show the efficacy of bismuth-based quadruple regimen for the first-line treatment of *H. pylori* infection.

## MATERIALS AND METHODS

### Patients

Local ethics committee approved the study. Informed consent was obtained from each patient. The study was performed in the patients with functional dyspepsia, who underwent upper gastrointestinal endoscopy, and completed therapy and the posttreatment *H. pylori* test. Exclusion criteria included, age <18 years, pregnancy or breastfeeding, anticoagulant treatment or coagulation disorders, previous gastric surgery, and treatment with antibiotics, PPI and bismuth compounds in the last 2 weeks.

### Methods

Upper gastrointestinal endoscopy was carried out in all patients. Two biopsy specimens were taken from gastric mucosa (antrum and corpus). The specimens were immediately fixed in neutral formalin and later routinely processed for histological examination. Four-micrometer-thick sections were prepared from each specimen. Sections from all patients were stained with hematoxylin-eosin and modified Giemsa. *H. pylori* infection was diagnosed with the demonstration of curved, spiral-shaped rods under light microscope.

The patients infected with *H. pylori* were treated with a 7-day bismuth-based quadruple therapy (esomeprazole 20 mg bid, colloidal bismuth subcitrate 600 mg bid, tetracycline 500 mg qid, and metronidazole 500 mg tid).

All patients were retested with C14 urea-breath test (Heliprobe, Kibion AB Uppsala, Sweden) at 6 to 8 weeks after treatment completion to confirm their *H. pylori* status. Acid suppressive drugs were stopped at 1 week before the test. After overnight fasting, patients swallowed an encapsulated form of C14-urea/citric acid. Breath samples were collected with a special dry cartridge system at 10 minutes. Patients exhaled gently into the cartridge mouthpiece until the color of the indicator membrane changed from orange to yellow. The breath card was inserted into a special small desktop-Geiger-Müller counter and activity was counted for 250 seconds. Results were expressed as counts per minute (CPM), and graded (0: not infected, CPM < 25; 1: equivocal, CPM 25-50; 2: infected, CPM > 50) as suggested by the manufacturer. Grade 0 was recognized to be *H. pylori* negative; grades 1 and 2 was to be *H. pylori* positive.

## Statistics

All statistical calculations were performed using SPSS (statistical package for social science) statistical program version 15.0. The treatment efficacy was determined by per protocol (PP) analysis. The patients who took at least 80% of the study medications and retested with C14 urea-breath test were included in analyses. Data were demonstrated as mean  $\pm$  standard deviation (SD) and compared by the Student's t-test for continuous variables. Categorical variables were reported as number and percent and compared using  $\chi^2$ -test. A p-value of <0.05 was taken to be significant.

## RESULTS

The study was performed in total 115 patients including 71 female (61.7%), 44 male (38.3%) who completed therapy and the post-treatment urea-breath test. The mean age was  $43.83 \pm 12.2$  years; the youngest patient was 18 and the oldest one was 64 years old. No patient discontinued the treatment of *H. pylori* eradication because of the side effects of drugs.

The results of posttreatment test for *H. pylori* were negative in 100 of 115 (87%) patients. Eradication rates of *H. pylori* were 93% (41/44) for male, 83% (59/71) for female. The treatment successes were similar between gender groups ( $p > 0.05$ ).

## DISCUSSION

*H. pylori* infection is one of the world's most common chronic infections and affects people of all ages. This

microorganism causes chronic active gastritis, the development and recurrence of peptic ulcer disease, and plays an important role in the development of gastric adenocarcinoma and MALT lymphoma.

Most widely used therapy for *H. pylori* eradication in all over the world is clarithromycin-based triple therapy (PPI + clarithromycin + amoxicillin) for at least 1 week. The success of this treatment regimen has gradually decreased because of increasing resistance to clarithromycin. The use of new treatment regimes in the first-line *H. pylori* eradication is mandatory for the improvement of eradication rates. In the recent past, bismuth-based quadruple therapy was used as second-line therapy for the situations where *H. pylori* eradication failed with triple therapy.<sup>8,9</sup> The use of bismuth-based regimens as first-line therapy in last years is also recommended.<sup>8,10,11</sup>

The resistance to clarithromycin in Turkey was reported to be over 40%.<sup>6,12</sup> It may be mentioned in the recommendation of 'Maastricht III Consensus Report' that stated 'The threshold of clarithromycin resistance at which attributed this antibiotic should not be used, or a clarithromycin susceptibility test should be performed, is 15 to 20%'.<sup>8</sup>

Songur et al reported eradication rates for standard therapy with clarithromycin and quadruple therapy with bismuth PP are 36 and 55% respectively.<sup>13</sup> Although bismuth-based quadruple regimen achieved higher eradication rate, the successes of both combinations were below the expectations.

In another study from Turkey, Uygun et al gave clarithromycin-based triple regimen and bismuth-based quadruple regimen for 14 days and their eradication rate were PP 63 and 83% respectively.<sup>14</sup> Although eradication time was 7 days in our study, the eradication rate was higher than that of Uygun et al (87 vs 83%). All of our patients received their therapy correctly because we gave detailed information to patients about drug use and possible side effects before the therapy.

In Dehghani's study; eradication rate was found to be 92% in age 18 and below population with bismuth-based quadruple regimen.<sup>15</sup> It must be remembered that resistance to antibiotics in pediatric group will be lower than the adults. In this trial, this was also observed. Ching et al obtained 97% eradication rate with 7 day bismuth-based quadruple regimen.<sup>16</sup>

In the past, levofloxacin/moxifloxacin-based triple regimens, sequential therapies and rifabutin-based triple regimens were recommended as second- or third-line therapy. Nowadays, these regimens are being used as first-line therapy. In a meta-analysis, it was found that levofloxacin-based triple regimen is more effective and more tolerable than standard clarithromycin-based regimen.<sup>17</sup>

Nista et al reported that the eradication in around 90% of patients was achieved with moxifloxacin-based regimen like levofloxacin-based regimen.<sup>18</sup> The eradication rates of moxifloxacin-based triple therapy in Turkey are very low; PP analysis 46% eradication rate was found in a study.<sup>19</sup> Sequential therapies are just new. Conflicting results have been reported in the literature.<sup>20-22</sup> The most important problem of sequential treatments is patient compliance. These treatments may be recommended for only selected patients. Rifabutin is an antibiotic which is used for tuberculosis treatment. The use of rifabutin is not appropriate in first-line *H. pylori* eradication because of the risk of cross-resistance to rifampicin.<sup>23-25</sup>

The triple therapies with ranitidine bismuth citrate had been used widely. It did not have any significant superiority to standard triple regimens. However, the eradication rates were a little higher when metronidazole was preferred to amoxicillin.<sup>26,27</sup> Ranitidine bismuth citrate is not marketed in Turkey any more.

Drug options used in past years have begun to change. The increase in clarithromycin resistance throughout the world and our country has forced physicians to look for new treatment options. One of these options, quadruple therapy containing bismuth may be effectively in the first-line *Helicobacter pylori* eradication.

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