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ORIGINAL ARTICLE

Different bismuth-based therapies for eradicating *Helicobacter pylori*: Randomized clinical trial of efficacy and safety

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Summary

Background and objective: Bismuth salts are used for treating dyspepsia, and they exert antibacterial effects on *Helicobacter pylori*. This study aimed to compare the efficacy and safety of three bismuth-containing combination regimens for *H. pylori* eradication in a Turkish population.

Methods: In this single-center study, 149 patients, who were diagnosed with *H. pylori* infection with urea breath test and histopathological examination, were randomized to receive the following therapies for 14 days: (1) bismuth-containing clarithromycin-based triple therapy (CBS-LAC), (2) bismuth-containing levofloxacin-based triple therapy (CBS-LAL), and (3) bismuth-containing quadruple therapy (BCQT). Eradication rates were evaluated six weeks after the treatment by performing intention to treat (ITT) and per protocol (PP) analyses. In addition, data on side effect profiles and patient compliance were collected.

Results: PP and ITT analyses showed that eradication rates were 86% and 81.1%, respectively, with BCQT; 68.3% and 66.7%, respectively, with CBS-LAL therapy; and 65.3% and 59.3%, respectively, with CBS-LAC therapy. Eradication rates obtained using PP and ITT analyses were statistically significant for all the regimens.

Conclusion: Addition of bismuth to standard triple and levofloxacin-based regimen did not show an acceptable increase in eradication rates. Therefore, BCQT may be preferred for the first-line treatment of *H. pylori* infection.

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Introduction

Helicobacter pylori (*H. pylori*) is a bacterial pathogen that causes many gastroduodenal diseases such as peptic ulcer, gastric cancer, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma [1,2]. Prevalence of *H. pylori* is 20%—50% in developed countries, and 80% in developing countries; prevalence of *H. pylori* infection varies from one country to another [1,2]. In Turkey, prevalence of *H. pylori* is 67.6—82.5% [3,4]. The eradication of these bacteria helps in preventing the recurrence of peptic ulcer, minimizing bleeding complications, and preventing the occurrence of gastric cancer and MALT lymphoma [5,6]. The eradication of *H. pylori* requires at least three or four multidrug combination therapies [7]. These therapies include drugs that lower stomach acidity, such as proton pomp inhibitors (PPI), and antibiotics such amoxicillin, clarithromycin, tetracycline, metronidazole or tinidazole, levofloxacin, moxifloxacin, furazolidone, rifabutin, and accompanying bismuth salts [7]. The efficacy of multidrug therapy depends on the susceptibility of *H. pylori* to antibiotics included in the therapy, duration of the therapy, doses of drugs included in the therapy, and compliance of patients [7].

Resistance to antibiotherapy is an important problem in *H. pylori* eradication. Consensus conferences have recommended therapeutic regimens that achieve eradication rates of >80% on an intention-to-treat (ITT) basis [8,9]. PPI, clarithromycin, and amoxicillin combinations are recommended as the first choice of therapy in patients who show <20% resistance to clarithromycin [6,8,10]. However, eradication rates with the standard triple therapy, which is the most commonly used treatment regimen for *H. pylori* eradication, have fallen below 80% because of an increase in macrolide resistance worldwide. [9,11]. Eradication rate with the standard triple therapy is 71% in the USA and 60% in western Europe [11]. Alternative regimens are recommended in regions where eradication rates are below 80% because of increasing resistance to macrolides.

Bismuth salts have been used for treating dyspepsia since the third century. Bismuth has been used in gastroenterology for treating stomatitis, diarrhea, peptic ulcer, and *H. pylori* infection [12]. Colloidal bismuth subcitrate (CBS), bismuth subsalicylate, and ranitidine bismuth citrate are the available forms of bismuth. Bismuth exerts an antibacterial effect on *H. pylori* via various mechanisms such as inhibition of cell wall, protein, and ATP synthesis; inhibition of cell membrane function; and inhibition of *H. pylori* binding to host cell surface [12,13]. Moreover, bismuth exerts cytoprotective and ulcer-healing effect and inhibits gastric acid secretion [12]. Bismuth monotherapy can eradicate *H. pylori*; however, the efficiency of eradication is low. Bismuth-containing regimens are recommended to patients showing clarithromycin and/or metronidazole resistance. Double, triple, and quadruple combination therapies of bismuth with antibiotics increase *H. pylori* eradication rates [8,14,15]. There are no reports of patients developing resistance to bismuth salts [16]. Moreover, side effects have been rarely reported among patients receiving bismuth therapy. Side effects such as heavy metal toxicity and encephalopathy are only observed in patients receiving long-term and high-dosage therapies [17].

Because clarithromycin resistance is high in Turkey, *H. pylori* eradication rates with standard regimens are low [18]. Moreover, increase in antibiotic resistance has decreased the therapy options available for eradicating *H. pylori* in developing countries such as Turkey. This has led researchers to identify new antibiotics or combination regimens for eradicating *H. pylori*. Therefore, this study aimed to evaluate the efficiency and reliability of bismuth-containing regimens for eradicating *H. pylori* by considering the antibacterial activity of bismuth and its synergistic effects with other antibiotics. For this, we performed a prospective randomized trial to compare the efficacies of the following 14-day bismuth-containing regimens to eradicate *H. pylori*:

- bismuth-containing quadruple therapy (BCQT);
- bismuth-containing clarithromycin-based triple therapy (CBS-LAC);
- bismuth-containing levofloxacin-based triple therapy (CBS-LAL).

Material and methods

This single-center, prospective, randomized control study was performed at the Gastroenterology Outpatient Clinic of the Ankara Oncology Education and Research Hospital from October 2012 to October 2013. This study was performed according to the recommendations of the Consort Statement and in compliance with the Helsinki Declaration. The study protocol was approved by the Ethics Committee for Human Studies of the Ankara Oncology Education and Research Hospital. Patients who visited the outpatient clinic for dyspepsia, family history of gastric cancer, and iron deficiency/anemia were enrolled into the study. Exclusion criteria were as follows: age <18 and >75 years; treatment with antibiotics, bismuth salts, nonsteroidal anti-inflammatory drugs (NSAIDs), PPIs, aspirin, or H_2 receptor blockers during 4 weeks before the study; alcohol consumption; use of systemic glucocorticoids; pregnancy; lactation; use of immunosuppressive drugs; coexisting gastric cancer; history of gastric surgery; allergy to any study medication; inability to undergo follow-up; chronic renal and hepatic failure; severe cardiopulmonary disease; malignant diseases; and history of *H. pylori* therapy. All the patients were informed about the possible common side effects of the treatments before the study and were asked to sign a consent form.

In addition to routine physical examination, age, gender, body mass index (BMI), smoking status, and primary complaints were recorded for all the patients. Indications for eradication were decided based on clinical, endoscopic, and histopathological findings. *H. pylori* infection status was determined using ^{14}C-urea breath test (^{14}C-UBT) and histopathological examination after upper gastrointestinal endoscopy and biopsy. Endoscopy was performed by the researchers (Drs. HG, IKO, EO). Two biopsy specimens were taken from the gastric antrum during endoscopy (from the greater and lesser curvature at 3 cm within the pyloric ring), and one biopsy specimen was taken from the gastric corpus along the greater curvature. ^{14}C-UBT (Shenzhen Zhonghe Headway Bio-Sci & Tech Co., Ltd.) was performed