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Comparison of bismuth-containing quadruple and concomitant therapies as a first-line treatment option for *Helicobacter pylori*

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Background/aims: *Helicobacter pylori eradication rates with standard triple regimens are worsening, and alternative treatments are urgently needed in some populations. The present study aimed to compare the efficacy of bismuth-based quadruple and concomitant regimens.* ***Methods:*** *Consecutive Helicobacter pylori-positive patients with non-ulcer dyspepsia were randomized to receive one of two regimens: (i) bismuth subsalicylate 300 mg q.i.d., esomeprazole 40 mg b.i.d., tetracycline 500 mg q.i.d., and amoxicillin 1 g b.i.d. (bismuth group) or (ii) esomeprazole 40 mg b.i.d., tetracycline 500 mg q.i.d., amoxicillin 1 g b.i.d., and metronidazole 500 mg t.i.d. (concomitant group) for 14 days. Gastroscopy and ^{14}C-urea breath test were performed before enrollment, and urea breath test was repeated six weeks after the treatment.* ***Results:*** *A total of 200 patients were randomized, and 180 of them completed the protocols. The intention-to-treat and per-protocol eradication rates were 79% (95% confidence interval 71-87) and 89.7% (95% confidence interval 83-95) in the bismuth group and 74% (95% confidence interval 68-81) and 80.4% (95% confidence interval 72-87) in the concomitant group. The bismuth regimen achieved a slightly better eradication rate compared to the concomitant group in both per-protocol and intention-to-treat analysis, but results were not statistically significant (p>0.05). Ten patients (6 in bismuth, 4 in concomitant groups) dropped out of the study because of side effects.* ***Conclusions:*** *The quadruple regimens with or without bismuth achieved moderate eradication rates as a first-line eradication option of Helicobacter pylori in our population, in which a bismuth-based regimen seems more appropriate. The compliance and side effects are important issues affecting the success of these regimens.*

Key words: Bismuth, concomitant, eradication, *Helicobacter pylori,* treatment

Birinci basamak *Helikobakter pilori* eradikasyonunda 'bizmut içeren dörtlü' ve 'eş zamanlı' tedavilerin karşılaştırılması

Amaç: *Helikobakter pilori eradikasyon oranları, standart üçlü rejimlerle giderek kötüleşmektedir ve bazı toplumlarda acilen alternatif tedavilere ihtiyaç vardır. Bu çalışma 'bizmut tabanlı dörtlü' ve 'eş zamanlı' rejimlerin eradikasyon etkinliğini karşılaştırmayı hedeflemektedir.* ***Yöntem:*** *Çalışmaya Helikobakter pilori pozitif, non-ülser dispepsili hastalar kabul edilerek, iki tedavi protokolünden birisine randomize edildi; birinci gruba 14 gün boyunca bizmut subsalisilat 300 mg q.i.d., esomeprazol 40 mg b.i.d., tetrasiklin 500 mg q.i.d. ve amoksisilin 1 g b.i.d. (bizmut grubu), ikinci gruba yine 14 gün esomeprazol 40 mg b.i.d., tetrasiklin 500 mg q.i.d., amoksisillin 1 g b.i.d. ve metronidazol 500 mg t.i.d. (eş zamanlı grup) tedavisi uygulandı. Tedavi öncesi Helikobakter pilori varlığı ^{14}C-Üre nefes testi ve endoskopik biyopsi ile saptandı, eradikasyonun kontrolü tedaviden 6 hafta sonra üre nefes testi ile yapıldı.* ***Bulgular:*** *Toplam 200 hasta gruplara randomize edildi ve bunların 180'i protokollerini tamamladı. Bizmut grubunda 'Intention-to-treat' ve 'Per-Protocol' eradikasyon oranları sırayla %79 (%95 CI 71-87) ile %89.7 (%95 CI 83-95) ve eş zamanlı grupta %74 (%95 CI 68-81) ile %80.4 (%95 CI 72-87) olarak bulundu. Bizmut rejimi, eş zamanlı grupla karşılaştırıldığında hem 'Per-Protocol' hem de 'Intention-to-treat' analizlerde hafifçe daha iyi eradikasyon oranları gösterdi; fakat sonuçlar belirgin istatistiksel anlam taşımıyordu (p>0.05). On hasta (6 bizmut, 4 eş zamanlı gruptan) yan etkiler nedeniyle çalışmadan ayrıldı.* ***Sonuç:*** *Bizmut içeren rejim biraz daha başarılı görülmekle beraber dörtlü rejimler, toplumumuzda birinci basamak Helikobakter pilori eradikasyonunda orta derecede eradikasyon başarısı göstermektedir. Tedaviye uyum ve yan etkiler, bu rejimlerin başarısını etkileyen önemli sorunlardır.*

Anahtar kelimeler: Bizmut, eş zamanlı, eradikasyon, *Helikobakter pilori,* tedavi

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INTRODUCTION

High eradication rates of Helicobacter pylori *(H. pylori)* with conventional proton pump inhibitors (PPIs)-based triple regimen have decreased significantly in recent reports, mostly due to increasing prevalence of antibiotic resistance (1-3). An epidemiologic analysis of trends over 10 years (1996-2005) in our population showed a gradual decrease in eradication success from 80% to 60% with standard PPI-based triple therapy (4). In the last few years, sequential-treatment regimens have been suggested as an effective first-line anti-*H. pylori* treatment and alternatives for standard triple regimens (5-7). However, the complexity of a sequential treatment regimen is an important disadvantage in routine practice, which threatens the compliance and also the success rate of this treatment.

The Maastricht III consensus meeting has accepted a bismuth-based quadruple regimen as an alternative first-line therapy (8). This regimen has achieved a better eradication rate compared to a PPI-based triple regimen as a first-line eradication option for *H. pylori* in our population (9). However, an important problem with this regimen is the limited availability of bismuth preparations in some countries. Non-bismuth-containing quadruple therapy with a PPI and three different antibiotics has been defined as "concomitant therapy" in a recent meta-analysis, which showed superiority of this approach over standard triple therapy (10). However, it is not clear yet if this approach might be used as a first-line treatment option in a population in which PPI-based triple therapy has failed. This study aimed to compare the effectiveness of a bismuth-containing quadruple therapy with non-bismuth-containing quadruple, or concomitant, therapy in the first-line eradication of *H. pylori*.

MATERIALS AND METHODS

Patients

Between March 2009 and March 2010, consecutive adult patients, naïve to *H. pylori* treatment, with endoscopy-proven, *H. pylori*-positive, non-ulcer dyspepsia were enrolled in the study if they tested positive for *H. pylori* on both urea breath test (UBT) and histology. The principal exclusion criteria were a previous attempt at *H. pylori* eradication and consumption of PPIs, (H_2)-receptor blockers, non-steroidal anti-inflammatory drugs, bismuth salts, or antibiotics within the previous four weeks. Pregnant or breastfeeding women and patients with a history of gastric surgery, presence of liver dysfunction or renal failure, alcohol abuse, and known allergy to the prescribed drugs were also excluded. Informed consent was obtained from each patient before enrollment, and the study protocol was approved by the local ethics committee. All subjects were free to withdraw from the study at any time in accordance with the guidelines of Good Clinical Practice and the principles of the Declaration of Helsinki (11).

Study Design and Treatment

This was a 14-day, open-label, prospective, parallel-arm, single-center study. After the enrollment procedure, all patients were randomly assigned into one of two study groups at a 1:1 ratio using random sampling numbers and sealed envelopes. The first group of subjects was administered a bismuth-based quadruple regimen with bismuth subsalicylate 300 mg q.i.d., esomeprazole 40 mg b.i.d., tetracycline 500 mg q.i.d., and amoxicillin 1 g b.i.d. (bismuth group). The second group of subjects was administered a quadruple treatment containing no bismuth compound but esomeprazole 40 mg b.i.d., tetracycline 500 mg q.i.d., amoxicillin 1 g b.i.d., and metronidazole 500 mg t.i.d. (concomitant group). Patient compliance was evaluated at the end of the treatment by pill count from the packet of the drugs, and was considered acceptable if more than 80% of the medication had been taken. Patients who were noncompliant were withdrawn from the study by the principal investigator. Patients were asked to report any adverse effects during the treatment period. Adverse effects were scored as mild, moderate or severe by investigators' assessments according to their effect on daily activities and the patients' discomfort, in response to open-ended questions. Antacids on demand were permitted, but no antibiotics, PPI or H_2-receptor blockers were allowed prior to the follow-up eradication test. Successful eradication of bacteria was defined as a negative UBT that was repeated six weeks after the end of treatment.

Histology

During the upper endoscopy, two biopsies were taken from the antrum and two from the gastric body. Biopsy specimens were fixed in 4% buffered formalin, embedded in paraffin wax, sectioned, and mounted on glass slides. Sections were stai-

ned with Giemsa and hematoxylin and eosin. Sections were reviewed by a single pathologist who was blinded to the endoscopic findings and UBT results. The activity of gastritis and density of *H. pylori* colonization were graded according to the updated Sydney system on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) (12). The presence of intestinal metaplasia was recorded as present or absent.

^{14}C-Urea Breath Test

The ^{14}C-UBT has been approved by the United States (US) Food and Drug Administration, and the standards have been defined by the Society of Nuclear Medicine. A low dose ^{14}C-UBT for the diagnosis of *H. pylori* infection was validated and compared with the standard method in a study by Ozturk et al. (13).

After an overnight fast, patients swallowed 37 kBq (1 mCi) of an encapsulated ^{14}C-urea/citric acid composition (Helicap, Noster System AB, Stockholm, Sweden) with 25 ml of water. Breath samples of patients were collected with a special dry-cartridge system (Heliprobe BreathCard, Noster System AB, Stockholm, Sweden) 10 minutes after administration. Patients exhaled gently into the cartridge mouthpiece until the indicator membrane changed in color from orange to yellow. The breath card was inserted into a small desktop Geiger-Muller counter (Heliprobe-analyzer, Noster System AB, Stockholm, Sweden), and activity was counted for 250 seconds. Results were expressed both as counts per minute (CPM) and as grade (0: not infected, CPM <25; 1: equivocal, CPM 25-50; 2: infected, CPM >50), as suggested by the manufacturer, according to the counts obtained from the cartridges. All procedures were done under the supervision of a specialist who was blinded to the study protocols.

Statistical Methods

According to the sample size for comparing event rates in independent case-control studies, the number of patients required for the study was calculated to detect a difference of 10% in the eradication rates between the two treatment protocols (Fisher's exact test). Based on a two-sided test, an alpha error level of 5% and a statistical power of 0.5, at least 87 patients per group were required for the per protocol (PP) analysis. Assuming a drop-out rate of 10%, at least 96 patients were needed to detect this difference. Results include the binominal 95% lower and upper confidence intervals (CI) (14).

The demographic and clinical features of the study groups were compared using the Wilcoxon rank sum test. Statistical analyses of the eradication frequency were made by chi-square test with a Yates correction and the Fisher's exact test when required. Both intention-to-treat (ITT) (all patients included in the protocols) and PP (the number of patients adherent to the protocol) population analyses were performed for eradication rates and comparisons. A p value less than 0.05 was considered statistically significant. All statistical analyses were performed using Microsta software (Ecosoft, Inc., Indianapolis, Indiana) and Microsoft Office Excel 2003 (Microsoft Corporation, Redmond, Washington).

RESULTS

Eight-hundred and fifty patients were screened, and 200 subjects were enrolled in the study. Other subjects were excluded because they were negative for *H. pylori,* did not meet inclusion criteria, or did not give their consent. Of the 200 patients enrolled, 180 completed their protocols independent of the results in full compliance with the study rules. Ten patients (5%) were lost to follow-up (bismuth group - 6, concomitant group - 4), and 10 patients (bismuth group - 6, concomitant group - 4) discontinued usage because of adverse effects. The baseline demographic and clinical characteristics of each group were comparable (Table 1). Eradication was achieved in 79 patients in the bismuth group and 74 patients in the concomitant group. The ITT and PP *H. pylori* eradication rates were 79% (95% CI 71-87) and 89.7% (95% CI 83-95) in the bismuth group, and 74% (95% CI 68-81) and 80.4% (95% CI 72-87) in the concomitant group (Figure 1). The bismuth regimen achieved a slightly better eradication rate compared to the concomitant group in both ITT (79% vs. 74%) and PP (89.7% vs. 80.4%)

Table 1. Demographic and clinical characteristics of the patients who completed the protocols

Characteristics/Groups	Bismuth	Concomitant	p
Number of patients, n	100	100	
Mean age (range), years	41.5 (18-68)	40.9 (19-72)	NS
Male/Female	59/41	53/47	NS
Smoking (>5 cigarettes/day)	21	26	NS
Alcohol use (>1 day/week)	8	5	NS
Antacids (as needed)	18	16	NS
Gastritis score (mean)	1.76±0.7	1.88±0.8	NS

NS: Non-significant.

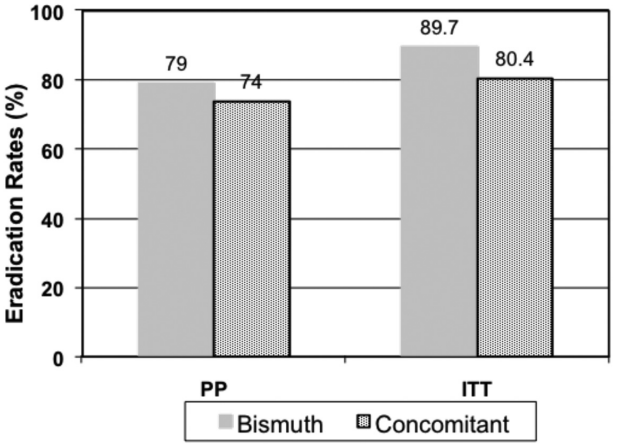

Figure 1. The per protocol and intention-to-treat eradication rates among groups.

analyses, but results were not statistically significant for either analysis (p>0.05).

Univariate analyses found no significant effect of sex, age, smoking, alcohol consumption, antacids usage, or gastritis score on the eradication rates. Mild intestinal metaplasia was detected in 4 patients from the bismuth group and in 5 patients from the concomitant group.

Ten patients (5%) reported moderate-to-severe adverse effects (bismuth group: abdominal discomfort and vomiting [n: 4] and diarrhea [n: 2]; concomitant group: abdominal discomfort and vomiting [n: 2], diarrhea [n: 1], and numbness [n: 1]), which caused significant discomfort and/or trouble in their daily activities. Treatment was discontinued in these patients and symptoms resolved completely in 2-9 days. No specific cause for these complaints was detected. A total of 14 (7%) patients complained of mild-to-moderate adverse effects (bismuth group: abdominal pain in 3, diarrhea in 2, alteration of taste in 1, and vaginal pruritus in 2; concomitant group: abdominal pain in 1, diarrhea in 2, alteration of taste in 2, and numbness in 1) that were attributed to the study drugs but did not require discontinuation. The prevalence of adverse effects did not differ significantly between the two groups. All of the mild-to-moderate adverse effects resolved in 1-6 days after the end of the study. The overall prevalence of reported adverse effects was 12% in all patients.

DISCUSSION

In this study, the bismuth-based quadruple regimen achieved an acceptable eradication success with 79% ITT and 89.7% PP eradication rates. This result was slightly better and more satisfying than the result of the concomitant therapy. In addition to their mucosal cytoprotective and ulcer-healing effects, the bismuth compounds have some complex actions on *H. pylori,* such as inhibition of ATP and protein synthesis and membrane function (15). They can suppress *H. pylori* in vivo when they are used alone, but the cure rate is low. However, their combination with two antibiotics significantly increases their efficacy on *H. pylori* and may overcome antibiotic-resistance in vivo and in vitro (16). The combination of bismuth subsalicylate or subcitrate with metronidazole and tetracycline or amoxicillin was the first traditional triple therapy for *H. pylori* eradication (17). However, because of the complexity and relatively high rate of adverse effects in this combination, it has mainly been surpassed by PPI-based triple regimens in the last decade. The challenge of imidazole and clarithromycin resistance in recent years brought renewed attention to this classical treatment. The addition of a PPI to this regimen, defined as a quadruple approach, has been suggested to decrease the frequency of adverse effects and increase the efficacy on *H. pylori* eradication (8,18). This regimen achieved a better eradication rate compared to a PPI-based triple regimen (82.3% vs. 62.7%, PP analysis, p<0.05) as a first-line eradication option for *H. pylori* in a recent study in our population (9). The eradication rate was 76.7% in ITT and 83.3% in PP analysis in a current placebo-controlled trial of bismuth-based quadruple treatment (19). In a recent meta-analysis of nine randomized controlled trials (RCTs), bismuth-containing quadruple therapy achieved eradication in 78.3% of patients as a first-line treatment (20).

Quadruple treatment of *H. pylori* with no bismuth compound but including a PPI and three different antibiotics has been defined as “concomitant” therapy by Essa et al. (10), since all drugs be given concomitantly as a non-sequential form. One important advantage of this regimen is general worldwide availability of all antibiotics compared to bismuth compounds. The concomitant approach is not standardized regarding the antibiotic selection or duration of treatment. For this reason, different results have been reported by various investigators. Essa et al. (10) analyzed the results of five RCTs that compared a concomitant approach with standard triple therapy, and they found that pooled estimates of the five RCTs showed superiority

of concomitant therapy over triple therapy with ITT and PP pooled odds ratio. According to their data, the concomitant therapy yielded excellent results, and duration of therapy became a significant variable, with longer duration tending to produce higher eradication rates. In our study, we preferred tetracycline instead of clarithromycin in the concomitant treatment arm. As dual resistance of *H. pylori* to metronidazole and clarithromycin has been seen in our population not rarely, we thought using them together would probably be a poor choice. The duration of treatment was also 14 days for both treatment arms in this study. Our previous experiences have shown that 7-10 day treatment with current eradication regimens does not achieve an optimum eradication rate (21). Since we assumed high antimicrobial resistance rates in our study, we preferred a 14-day regimen for empiric therapy.

Bismuth-containing quadruple therapy and concomitant therapy are among the current initial therapy options in populations in which PPI-based triple therapy has failed (22). In this study, the effectiveness of these two regimens has been compared for the first time. Although bismuth-containing quadruple therapy achieved better eradication rates in both ITT and PP analyses (79% vs. 74% in ITT and 89.7% vs. 80% in PP), the results were not statistically significant. The ITT eradication rates of both regimens were less than the generally accepted minimum eradication rate of anti-*H. pylori* treatment protocols. There was nearly a 10% difference between ITT and PP eradication rates with a bismuth- containing therapy, showing that side effects and compliance are very important in the eradication success of this treatment. The eradication rate of a 14-day PPI-based triple regimen is less than 60% in the current studies in our population (4,21). Thus, both regimens studied in this trial achieved a better *H. pylori* eradication rate than the PPI-based triple regimen in our population.

The frequency of adverse effects and compliance to treatment seem to be important factors affecting the treatment success of both regimens. However, we still consider a 10% drop-out rate as acceptable for such a complex and multidrug treatment.

In conclusion, bismuth-containing quadruple therapy and concomitant therapy are not ideal eradication regimens. However, it seems they achieve a significantly better eradication rate in our population than PPI-based triple regimen and might be used instead of this legacy triple therapy in the first-line treatment. Bismuth-containing treatment achieved a slightly better eradication rate than concomitant treatment for eradication of *H. pylori*; however, it presents some important problems with respect to side effects and compliance.

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