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Modified quadruple therapy versus bismuth-containing quadruple therapy in first-line treatment of Helicobacter pylori in Turkey

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Author’s contributions: study design: Ahmet Yozgat and Benan Kasapoğlu; data collection: Selim Demirci and Fevzi Coşkun Sökmen; data analysis: Selim Demirci and Fevzi Coşkun Sökmen; manuscript preparation: Ahmet Yozgat and Benan Kasapoğlu.

Conflict of interest: the authors declare no conflict of interest.

ABSTRACT

Aim: Helicobacter pylori (H. pylori) eradication is still an important issue in countries with high antibiotic resistance. This study aimed to compare the efficacy and safety of two bismuth-containing treatment modalities in H. pylori treatment in Turkey.
Material and methods: subjects with *H. pylori* infection who were treated with either bismuth-containing quadruple therapy (pantoprazole 40 mg bid, tetracycline 500 mg qid, metronidazole 500 mg tid, bismuth subcitrate 262 mg qid daily) (BQT group) or modified quadruple therapy (pantoprazole 40 mg bid, amoxicillin 1g bid, metronidazole 500 mg tid, bismuth subcitrate 262 mg qid daily) (MBQT group) for 14 days were compared, retrospectively. The eradication success rate, adverse events related to the medications and compliance were investigated.

Results: a total of 128 patients in the BQT group and 102 patients in the MBQT group completed the treatment. The overall rate of adverse events was significantly higher in the BQT group compared with the MBQT group (39.4 % vs 18.6; p: 0.001). Among the adverse events, nausea-vomiting and abdominal discomfort was significantly more frequent in the BQT group than in the MBQT group (p: 0.001). The adverse events were mild-moderate in both groups and life threatening adverse events were not present in any of the patients.

Conclusion: although both regimens were highly effective and safe in *H. pylori* eradication, both intention-to-treat (ITT) and per-protocol (PP) eradication rates were higher and adverse events were lower in the modified quadruple therapy group. Modified quadruple therapy should be kept in mind for the first-line treatment of *H. pylori* in regions with high clarithromycin and metronidazole resistance.

Keywords: *H. pylori*. Quadruple therapy. First-line treatment.

INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is a gram-negative bacterium. More than 50 % of the world population is affected by this pathogen, which causes a public health problem worldwide. The International Agency for Research on Cancer classified *H. pylori* as a carcinogen because it is associated with peptic ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma (1,2). Due to the increased prevalence of antimicrobial resistance of *H. pylori*, eradication success rates with standard treatment regimens have fallen worldwide (3-5).

In the Maastricht V Consensus Conference report, bismuth-containing quadruple treatments are suggested as the best alternative first-line treatment in populations with dual
clarithromycin and metronidazole resistance higher than 15 % (6). In recent studies, bismuth add-on regimens were defined as the most effective in the first line treatment of *H. pylori* infection (7).

Clarithromycin and metronidazole resistance are defined as the main factors in *H. pylori* eradication failure (8). In Turkey, high clarithromycin resistance rates reaching more than 40 % have been reported in previous studies (9,10). Metronidazole resistance is another important problem in *H. pylori* eradication worldwide, reaching more than 20 % in many countries, and metronidazole resistance was determined as more than 30 % in Turkey (11,12). However, for the eradication of *H. pylori*, the effects of high metronidazole drug resistance may be overcome by extending the treatment duration and escalating the administered dose (13). In a recent meta-analysis, Sezgin et al. investigated the mean eradication rates of the standard triple therapy (STT), consisting of standard doses of a proton pump inhibitor along with amoxicillin 1 g BID and clarithromycin 500 mg BID for 7-14 days in first-line *H. pylori* eradication in adults, in Turkey. A total of 45 studies and 3,715 patients were investigated in this analysis. The eradication rates reported according to the intention-to-treat (ITT) and per-protocol (PP) analyses were 60 % and 57 %, respectively (14).

Regarding these data, *H. pylori* eradication is still an important issue in countries with high clarithromycin and metronidazole resistance. This study aimed to compare safety and effectiveness of two bismuth-containing treatment modalities in *H. pylori* treatment, in Turkey.

**MATERIAL AND METHODS**

The study was performed in the Gastroenterology Department of the Dr Abdurrahman Yurtaslan Oncology Hospital, Ankara, Turkey. Subjects with *H. pylori* infection and treated with either bismuth-containing quadruple therapy or modified quadruple therapy for 14 days between March and October 2018 were retrospectively compared. Bismuth-containing quadruple therapy included pantoprazole, bismuth subcitrate, metronidazole and tetracycline (262 mg qid, 40 mg bid, 500 mg tid, 500 mg qid daily, respectively), and modified quadruple therapy included pantoprazole, amoxicillin, metronidazole and bismuth subcitrate (40 mg bid, 1 g bid, 500 mg tid and 262 mg qid daily, respectively). The eradication rate, side effects related to the medications and adherence were investigated.
H. pylori infection is diagnosed by histological examination of biopsies taken from patients during endoscopy. There is a routine protocol for the H. pylori eradication in our gastroenterology outpatient clinic. Patients diagnosed with an active H. pylori infection are asked about antibiotic resistance and informed about the treatment regimens and their adverse effects. All patients who are prescribed antibiotic treatment are asked to visit at the end of the treatment regimen (two weeks after enrollment) to check for adverse events, drug adherence, to adjust eradication success and to check for side effects after six weeks of therapy. Data were obtained from patient records and those with incomplete records were excluded from the study. The study was performed according to the guidelines for Good Clinical Practice and the Declaration of Helsinki (1996 version, amended October 2000). The Abdurrahman Yurtaslan Oncology Training and Research Hospital Local Ethics Committee approved the study (reference: 2019/447). Since the study was retrospective, informed consents could not be obtained, so the patient identification information was removed from the data analysis.

Patients previously treated with H. pylori, with an allergy to the medications, pregnant or breast-feeding women, patients with gastric cancer and a history of gastric surgery were excluded from the study.

Statistical analysis
Data were analyzed using the SPSS software for windows (IBM SPSS 20, IBM Corp., NY). Demographic features of the two groups were compared using the Chi-squared test. All patients had taken at least the first dose of started medications included and were assessed for the ITT analysis. Only those who continued and completed the treatment without violating the regulations (violation is < 80% treatment compliance) were included and assessed for the PP analysis. p < 0.05 was considered as statistically significant.

RESULTS
A total of 278 patients were investigated. Among those, 34 patients were excluded due to missing data in their medical records. Thus, 244 patients (142 in the bismuth quadruple therapy [BQT] group and 102 in the modified Bismuth quadruple therapy [MBQT] group) were included in the analyses. Demographic features of the study participants are
summarized in table 1. A total of 128 patients in the BQT group and 102 patients in the MBQT group completed the treatment (Table 2). The intention to treat analysis showed 81.69% and 88.23% in the BQT group and the MBQT group, respectively. Per protocol analysis revealed 90.62% and 95.74% in the BQT group and the MBQT group, respectively. The incidence of adverse events is summarized in table 3. Compared with the MBQT group, all side effects were more common in the BQT group. The overall rate of adverse events was significantly more common in the BQT group compared with the MBQT group (p: 0.001). Among the adverse events, nausea-vomiting and abdominal discomfort were significantly more common in the BQT group than in the MBQT group (p: 0.001). The adverse events were mild and moderate in both groups and no life-threatening adverse event were identified in any of the patients.

DISCUSSION

In this study, the eradication rates of bismuth-containing quadruple therapy and modified bismuth-containing quadruple therapy were all high enough to be defined as effective. Eradication rates of ITT and PP were higher in the MBQT group than in the BQT group, but the differences were not statistically significant. The adverse events associated with these treatment modalities were generally more common in the BQT group.

In Turkey, bismuth-containing regimens are generally recommended for the eradication of H. pylori infection due to the resistance of clarithromycin and metronidazole. The most preferred and recommended treatment modality is the BQT. In previous literature, there are many studies that report the efficiency of this treatment. Gao et al. reported eradication rates of 86.7% for ITT and 94.5% for PP in 120 patients with known penicillin allergies (15). Salmanroghani et al. (16) compared the efficacy and tolerability of tetracycline with high-dose amoxicillin (1,000 mg three times a day) in bismuth-based quadruple therapy. The reported eradication rate was higher with the amoxicillin-containing regimen than with the tetracycline-containing regimen (95.51% vs 83.8% by per-protocol analysis and 92.9% vs 76.5% by intention-to-treat analysis). Castro Fernández et al. (17) reported that treatment compliance was 96% with the three-in-one capsule formulation containing bismuth subcitrate, metronidazole and tetracycline, and adverse effects were reported in 28.5% of patients. The effectiveness of this treatment based on
intention to treat was 91.5 % and per protocol was 95.2 %. Very recently, Alsamman et al. (18) compared different treatment modalities in H. pylori eradication including quadruple, triple and doxycycline quadruple regimens and reported that quadruple therapy for 14 days was the best. Modified quadruple therapy was defined as an alternative for this treatment with high cure rates. Zhang et al. (19) compared the efficacy and tolerability of 14-day modified bismuth quadruple therapy (lansoprazole, amoxicillin, bismuth potassium citrate, with metronidazole or clarithromycin) and both regimens were highly effective. Cure rates of ITT and PP were 96.9 % and 88.9 % in the metronidazole administered group, respectively. Choe et al. (20) reported cure rates with 14-day bismuth containing quadruple therapy of 88.1 % by ITT and 96.6 % by PP analysis, and defined this as an alternative to triple therapy for the first-line eradication. Chen et al. (21) reported that both empiric modified bismuth quadruple therapy and susceptibility-guided therapy were highly effective with ITT rates of 85.4 % and 91.6 %, respectively, and 97.6 % and 97.7 % for the per-protocol eradication rates. The difference was not statistically significant. The data comparing these two regimens is limited in previous literature. Chen et al. (22) compared bismuth-containing quadruple therapies with tetracycline or amoxicillin for rescue treatment of H. pylori and reported that the ITT and PP rates were 88.5 % and 93.7 % for amoxicillin and 87.2 % and 95.3 % for tetracycline groups, respectively. Furthermore, compliance was higher and adverse events were less common in the amoxicillin group than in the tetracycline group. Our findings also support these data. Lim et al. (23) started a multicenter, randomized and open-label trial comparing quadruple therapy with modified bismuth therapy in Korea and the results have not been reported yet.

In this study, the overall adverse effects were significantly more common in the BQT group compared with the MBQT group (39.4 % vs 18.6 %). Gao et al. (15) reported mild to moderate adverse effects in 46.7 % of patients and Jheng et al. (24) reported adverse events in 22.2 % of patients treated with BQT. Choe et al. (17) reported an adverse events rate of 23 % in patients treated with MBQT. Our results were also compatible with the previous literature regarding adverse events rates.

There are some limitations of this study that should be mentioned. First, this is a retrospective study performed in a single tertiary hospital. Phenotypic or genotypic
antibiotic resistance testing was not performed, which was the main limitation of the study. Different time periods of treatments were not analyzed which may be the topic of another study.

**CONCLUSION**
The efficiency and safety profiles of bismuth-containing treatment regimens, quadruple therapy and modified quadruple therapy were compared in Turkey. Although both regimens were highly effective and safe for *H. pylori* eradication, both ITT and PP eradication rates were higher and adverse events were lower in the modified quadruple therapy group. Modified quadruple therapy should be kept in mind for *H. pylori* first line therapy in regions with high resistance to metronidazole and clarithromycin treatment.

**REFERENCES**


Table 1. Demographic and clinical characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>BQT group (n = 142)</th>
<th>MBQT group (n = 102)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>56/86</td>
<td>42/60</td>
<td>0.714</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.21 ± 7.42</td>
<td>48.62 ± 8.64</td>
<td>0.821</td>
</tr>
<tr>
<td>Smoking habit (%)</td>
<td>98 (69.01)</td>
<td>69 (67.67)</td>
<td>0.854</td>
</tr>
</tbody>
</table>

BQT: bismuth quadruple therapy; MBQT: modified bismuth quadruple therapy; M: male; F: female. Age is presented as the mean ± SD (Student’s t test); gender, smoking habit (Chi-squared test); p < 0.05.
Table 2. Treatment compliance, *H. pylori* eradication rates and drug adverse effects

<table>
<thead>
<tr>
<th></th>
<th>BQT group (n = 142)</th>
<th>MBQT group (n = 102)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion of treatment (%)</td>
<td>128 (90.14%)</td>
<td>94 (92.15%)</td>
<td>0.151</td>
</tr>
<tr>
<td>Rate of eradication</td>
<td>116</td>
<td>90</td>
<td>0.121</td>
</tr>
<tr>
<td>ITT (95% CI)</td>
<td>81.69 (75.9-88.1%)</td>
<td>88.23 (80.8-93.9%)</td>
<td>0.210</td>
</tr>
<tr>
<td>PP (95% CI)</td>
<td>90.62 (85.5-95.7%)</td>
<td>95.74 (91.5-99.8%)</td>
<td>0.121</td>
</tr>
</tbody>
</table>

BQT: bismuth quadruple therapy; MBQT: modified bismuth quadruple therapy; ITT: intention-to-treat; PP: per-protocol. Chi-squared test.
Table 3. Drug adverse effects

<table>
<thead>
<tr>
<th></th>
<th>BQT group (n = 142)</th>
<th>MBQT group (n = 102)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>8 (5.6)</td>
<td>4 (3.9)</td>
<td>0.561</td>
</tr>
<tr>
<td>Nausea ± vomiting</td>
<td>26 (18.3)</td>
<td>9 (8.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Metallic taste</td>
<td>21 (14.7)</td>
<td>15 (11.7)</td>
<td>0.681</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>24 (16.9)</td>
<td>6 (5.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (11.2)</td>
<td>9 (8.8)</td>
<td>0.232</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (9.8)</td>
<td>8 (7.8)</td>
<td>0.412</td>
</tr>
<tr>
<td>Total</td>
<td>56 (39.4)</td>
<td>19 (18.6)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

BQT: bismuth quadruple therapy; MBQT: modified bismuth quadruple therapy. Chi-squared test.