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Bismuth-based therapies for the first step eradication of *Helicobacter pylori*

Birinci basamak *Helicobacter pylori* eradikasyonunda bizmut esasl› tedaviler

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Background/aims: *Combination of a proton pump inhibitor, amoxicillin, and clarithromycin, which have been recommended as a primary treatment for Helicobacter pylori (H. pylori) infection, provides eradication in approximately 50% of cases of H. pylori infection in Turkey. There is no effective eradication regimen for H. pylori in our country. We aimed to compare bismuth-based triple and quadruple treatments for eradication of H. pylori.* ***Methods:*** *Eighty-two patients were enrolled into the study between October 2002 and August 2003. The patients were randomly assigned into two groups. One group received ranitidine bismuth citrate 2x400 mg, metronidazole 3x500 mg and tetracycline 2x1000 mg for 14 days (RMT group) and the other group pantoprazole 2x40 mg, bismuth subcitrate 4x300mg, amoxicillin 2x1000 mg and clarithromycin 2x500 mg for 14 days (PBAC group). The eradication was assessed four weeks after completion of the treatment, and the patients underwent endoscopy and were asked whether there were changes in their symptoms. When H. pylori was negative on both histological examination and urease test, the disease was considered eradicated.* ***Results:*** *H. pylori was eradicated in 26 of 42 patients in the RMT group (61.9%) and in 22 of 40 patients in the PBAC group (55%). In total, eradication was achieved in 48 out of 82 patients (58.5%). There was no significant difference in eradication between the groups.* ***Conclusion:*** *Neither regimen (RMT or PBAC) was effective in eradicating H. pylori infection in our area. Further investigations are needed.*

Key words: *Helicobacter pylori*, eradication, bismuth

Amaç: *Helicobacter pylori (H. pylori) eradikasyonu için birinci basamakta tedavi olarak önerilen proton pompa inhibitörü, amoksisilin ve klaritromisin tedavisi ülkemizde ancak %50 civarında eradikasyon sağlamaktadır. Etkin eradikasyon tedavisi arayışlarımız devam etmekte olup bu amaçla H. pylori eradikasyon başarısını artırdığı bilinen bizmut esaslı 3'lü ve 4'lü tedavileri ilk basamak tedavide karşılaştırmayı amaçladık.* ***Yöntem:*** *Ekim 2002 ve Ağustos 2003 arasında şikayeti nedeniyle endoskopi yapılıp üreaz testi veya histopatolojik olarak H. pylori pozitif olan 82 hasta çalışmaya dahil edildi. Hastalar rastgele iki gruba ayrılarak birinci gruba ranitidin bizmut sitrat 2x400 mg, metronidazol 3x500 mg, tetrasiklin 2x1000 mg (RMT) ve ikinci gruba pantoprazol 2x40 mg, bizmut subsitrat 4x300mg, amoksisilin 2x1000 mg, klaritromisin 2x500 mg (PBAK) 14 gün süreyle verildi. Tedavi bitiminden 4 hafta sonra H. pylori eradikasyonu endoskopileri tekrarlanarak değerlendirildi. Semptomlardaki değişim açısından sorgulandı. Histoloji ve üreaz testi ile H. pylori negatifse eradikasyon olarak kabul edildi.* ***Bulgular:*** *RMT grubundaki 42 hastanın 26'sında %61.9 ve PBAK grubundaki 40 hastanın 22'sinde %55 oranında eradikasyon sağlandı. Toplam olarak 82 hastadan 48'inde (%58.5) eradikasyon sağlandı. İki grup arasında eradikasyon oranları açısından istatistiki olarak anlamlı fark bulunmadı.* ***Sonuç:*** *Hem RMT hem de PBAK H. pylori eradikasyonunda etkili bir kombinasyon olarak bulunmadı.Bu konuda ileri araştırmalara gerek vardır.*

Anahtar kelimeler: *Helicobacter pylori*, eradikasyon, bizmut

INTRODUCTION

Helicobacter pylori (*H. pylori*), the most common infectious disease, is associated with peptic ulcer, atrophic gastritis, MALT lymphoma and adenocarcinoma of the stomach (1-3). Turkey has a high rate of *H.pylori* prevalence, reported as approximately 81% (4-6). Therefore, both *H.pylori* infection and results and treatment are a significant health problem. Although a wide variety of treatment regimens are available at present, an ideal treatment for eradication of *H.pylori* has not been determined. Preferred treatment regimens were monotherapies in the 1990s, later becoming triple and quadruple treatments. According to the Maastricht Consensus Report declared in 2000, primary treatment for eradication of *H.pylori* should include a proton pump inhibitor (PPI) or ranitidine bismuth citrate (RBC) plus two antibiotics (amoxicillin, metronidazole or clarithromycin) (7).

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The treatment should last for at least seven days. Unfortunately, eradication schemes including PPI, amoxicillin, and clarithromycin have demonstrated disappointing results. Eradication rates with these schemes were reported as 50-60% (8-17). A part of some studies from Turkey have shown that addition of bismuth salts to therapy increased the eradication rate of *H.pylori* (12, 18, 19).

In the present study, we investigated the role of bismuth-based therapies in the eradication of *H.pylori* in the first step.

MATERIALS AND METHODS

This study included 82 patients who underwent endoscopy for investigation of dyspepsia and were found to be *H.pylori*-positive between October 2002 and August 2003. All patients gave informed consent. The patients who suffered from a serious illness; those who underwent previous gastric surgery; diabetics; those who received antibiotics, H-2 receptor blockades, bismuth or PPI during the past two months; and those who were previously given treatment for eradication of *H.pylori* were not included in the study. They were randomized into two groups to receive either RBC 2x400 mg, metronidazole 3x500 mg and tetracycline 2x1000 mg for 14 days (RMT group) or pantoprazole 2x40 mg, bismuth subcitrate 4x300 mg, amoxicillin 2x1000 mg and clarithromycin 2x500 mg for 14 days (PBAC group). History was taken from all patients. They were also subjected to physical examination and routine laboratory investigations. The treatments received by the patients were recorded. The symptoms (epigastric pain, distension, nocturnal pain and pyrosis) were rated according to Likert's Scale (0=none, 1=mild, 2=moderate, 3=severe and 4=quite severe). Two biopsy specimens from the antrum and two from the corpus were taken for pathological examinations, and one biopsy specimen from the antrum was taken for urease test. We used urease test prepared in the microbiology laboratory of our hospital. Results of pathological examinations were evaluated according to Sidney classification. Four weeks after completion of the treatments, side effects of the treatments and changes in patients' symptoms were evaluated and endoscopic examinations were repeated by a gastroenterologist. Same endoscopic procedures were performed. When *H.pylori* was negative on both histological examinations and urease test, the disease was considered eradicated. If one of them was positive, eradication was considered unsuccessful.

Compliance with the treatment was investigated: patients who took their drugs every day were considered 100% compliant; those who forgot to take their drugs for one, two, or three days or more were considered 80-99%, 60-79% and below 59% compliant, respectively. Any side effects which prevented the patients from taking their drugs were also recorded.

Statistical Analysis

Chi-square test was used to determine the difference in eradication between the groups. Independent-t test was used for determination of difference in age and two proportions test for the difference in gender, smoking and the use of NSAIDs. SPSS (version 11.5) and MINITAB package programs were utilized.

RESULTS

The study included 82 patients (49 female, 33 male). The patients were aged between 18 and 74 years, with a mean age of 46.6±12.3 years. Demographic features of the patients are shown in Table 1. There was no significant difference in age, gender, smoking, and NSAIDs use between the groups. Endoscopic findings of the patients are shown in Table 2. Forty-two patients were assigned into the RMT group and 40 patients into the PBAC group. One patient in the RMT group had nausea and therefore took his drugs for only 10 days; another patient in the same group took his drugs for 13 days after forgetting one day. Two patients in the PBAC group had side effects (acrid taste,

Table 1. Demographic features of patients

	RMT group	PBAC group
Age (mean)	47.4 years	45.8 years
Gender (M/F)	19/23	14/26
Smoking	12/42	14/40
NSAIDs use	18/42	20/40

Table 2. Lesions detected on endoscopy

Endoscopic Lesions (n=82)	n
Normal	2 (2.4%)
Antral gastritis	32 (39%)
Pangastritis	24 (29.2%)
Erosive gastritis	5 (6%)
Atrophic gastritis	6 (7.3%)
Alkaline reflux gastritis	11 (13.4%)
Gastric ulcer	2 (2.4%)
Esophagitis	7 (8.5%)
Bulbitis	17 (20.7%)
Duodenal ulcer	6 (7.3%)
Duodenitis	2 (2.4%)

diarrhea), each taking their drugs for 12 days. The eradication was achieved in 26 patients (61.9%) in the RMT group and in 22 patients (55%) in the PBAC group. There was no significant difference in the rate of eradication between the groups (p=0.526).

DISCUSSION

At present, treatments including PPI are used in all steps of *H.pylori* eradication. Although the recent regimens of antibiotics have achieved high rates of *H.pylori* eradication, in the western literature, 10-20% of patients still remain infected following the primary treatment (20). However, eradication results with these regimens have been disappointing in our country (8-17). Similarly, some European studies have revealed low rates of eradication with the standard triple treatment regimen (21-24). In one study, we also found low rates of eradication with a triple treatment regimen including PPI, amoxicillin, and clarithromycin (8), which forced us to investigate alternative treatments for eradication of *H.pylori*.

Conflicting rates of eradication with the same treatment regimens reported in the literature suggest that resistance to antibiotics, virulence factors of *H.pylori* and the type of gastroduodenal disease may play a role in eradication of *H.pylori*. In fact, some studies reporting low rates of eradication have also revealed a high resistance to clarithyromycin (10%) (25). Studies performed in Turkey shown a high resistance rate to metronidazole and clarithromycin. We found 11% clarithromycin resistance by polymerase chain reaction (PCR) (26). Another group has reported similar findings (27). Also, a higher rate for resistance to clarithromycin (56%) (28) and high metronidazole resistance (29) have been reported.

Bismuth salts have been used for the treatment of gastritis and peptic ulcer for over two centuries (30). Bismuth exerts a direct bactericidal effect on *H.pylori*. However, RBC inhibits acids, protects the mucosa and has an antimicrobial effect on *H.pylori* (31). To date, no resistance to bismuth has been reported (30).

We used bismuth subcitrate and pantoprazole in one group of patients (PBAC group) and RBC in the other group (RMT group).

In a study in Italy on omeprazole, bismuth subcitrate, tetracycline and metronidazole, the rate of eradication was 95% (30). In one study from the United States, RBC, amoxicillin and clarithromycin were reported to achieve eradication in 75% of the patients (31). In another study from the US, bismuth, lansoprazole, amoxicillin and clarithromycin had an eradication rate of 85% (32). Thus, treatment regimens including bismuth have resulted in various rates of eradication.

In the present study, the rate of eradication was 61.9% in the RMT group and 55% in the PBAC group. In fact, the obtained rates of eradication were quite low, although patient compliance with the treatment regimens was high. It may be that most of the patients had non-ulcer dyspepsia. In fact, it has been reported that the rates of eradication are lower in cases of non-ulcer dyspepsia than in cases of peptic ulcer (25). In a well-designed study from Ankara, Turkey, similar low eradication rates have been reported (32). In the RBC, amoxicillin, and clarithromycin group, the eradication rate was 66%, and in the RBC, tetracycline, and metronidazole group, it was 59%.

In conclusion, no standard treatment regimen has been found to date which will achieve a high rate of *H.pylori* eradication in our region.

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