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Effectiveness of different treatment regimens in *helicobacter pylori* eradication: Ten-year experience of a single institution

Helikobakter pilori eradikasyonunda farklı tedavi protokollerinin etkinliği "son on yıl verilerimiz"

Ali ÖZDEN, Gülseren SEVEN, Mehmet BEKTAŞ

Department of Gastroenterology, Ankara University School of Medicine, Ankara

Aim: *We aimed to report the outcomes of different H. pylori eradication regimens used in our institution over the last 10 years.* ***Method:*** *Retrospectively, H. pylori-positive patients who were referred for upper gastrointestinal endoscopy with dyspeptic symptoms and who started eradication treatment and returned for a follow-up visit were included in the study. Subjects were allocated into six groups according to their treatment regimens as follows: Group 1) Proton pump inhibitor, clarithromycin and amoxicillin for 2 weeks; Group 2) Colloidal bismuth subcitrate, metronidazole and tetracycline for 2 weeks; Group 3) ranitidine bismuth citrate, clarithromycin and amoxicillin for 2 weeks; Group 4) Proton pump inhibitor, colloidal bismuth subcitrate, clarithromycin and amoxicillin for 2 weeks; Group 5) Proton pump inhibitor, tetracycline and amoxicillin for 2 weeks; and Group 6) Proton pump inhibitor and amoxicillin for 5 days, followed consecutively by Proton pump inhibitor, clarithromycin and metronidazole for 5 days. A follow-up visit to determine eradication was scheduled a minimum of 6 weeks after completion of the treatment.* ***Results:*** *In this study, 400 patients were included. Eradication rates were 74.7%, 92.3%, 81.2%, 81.5%, 70.5%, and 66.6% in Groups 1-6, respectively.* ***Conclusion:*** *In Group 1, the eradication rate was lower than 80%. In Groups 3-4, the eradication rate increased to over 80%. The colloidal bismuth subcitrate, metronidazole and tetracycline regimen (Group 2) was the most successful, with a rate of 92.3%. The eradication rate in the consecutive regimen group (Group 6) did not reach the recommended level (higher than 80-85%).*

Key words: *Helicobacter pylori,* eradication

Amaç: *Çalışmamızdaki amaç son on yılda farklı tedavi seçenekleri ile H. pilori eradikasyonunda elde ettiğimiz verileri sunmaktır.* ***Yöntem:*** *1999 ile 2009 yılları arasında dispeptik yakınmaları nedeniyle üst gastrointestinal sistem endokopisine refere edilen, H. pilori pozitif, eradikasyon tedavisi alan ve tedavi sonrası kontrolü yapılan hastalar retrospektif olarak değerlendirildi. Grup-1) proton pompa inhibitörü 2x1, klaritromisin 500 mg 2x1, amoksisilin 1000 mg 2x1, 2 hafta; Grup-2) kolloidal bizmut subsitrat 300 mg 4x1, metronidazol 500 mg 3x1, tetrasiklin 500 mg 3x1 2 hafta süre; Grup-3) ranitidin bizmut sitrat 400 mg 2x1, klaritromisin 500 mg 2x1, amoksisilin 1000 mg 2x1 2 hafta; Grup-4) proton pompa inhibitörü 2x1, kolloidal bismuth subsitrat 300 mg 4x1, klaritromisin 500 mg 2x1, amoksisilin 1000 mg 2x1, 2 hafta; Grup-5) proton pompa inhibitörü 2x1, tetrasiklin 500 mg 3x1, amoksisilin 1000 mg 2x1, 2 hafta; Grup-6) proton pompa inhibitörü 2x1, amoksisilin 1000 mg 2x1/5 gün ve proton pompa inhibitörü 2x1, klaritromisin 500 mg 2x1, metronidazol 500 mg 2x1/ 5 gün süre ile aldılar. Eradikasyon belirlenmesi için kontrol, tedavi bitiminden en erken 6 hafta sonra yapıldı.* ***Bulgular:*** *Çalışmada 400 hasta yer aldı. Eradikasyon oranları sırayla %74.7, %92.3, %81.2, %81.5, %70.5 ve %66.6 olarak saptandı.* ***Sonuç:*** *Grup 1'de eradikasyon oranı %80'den düşük saptandı. Grup 3-4'te başarı %80 üzerine çıktı. Kolloidal bizmut subsitrat, metronidazol ve tetrasiklin (Grup 2) kombinasyonunda %92.5 eradikasyon oranı ile en yüksek başarı elde edildi. Ardışık tedavi (Grup 6) ile eradikasyon oranı kabul edilebilir oranların (>%80-85'ten fazla olması) altındaydı. H. pilori eradikasyonunda %80'nin üzerinde eradikasyon yalnız bizmut içeren 3'lü ve 4'lü tedavilerde elde edilmiştir.*

Anahtar kelimeler: *Helikobakter pilori,* eradikasyon

INTRODUCTION

Prevalence of *Helicobacter pylori (Hp)* infection in adults varies in different parts of the world depending on the social and economic standards of the population (1, 2). While the prevalence among the middle-aged population in developing countries is about 80%, it is only 20-50% in developed countries. The reported prevalence of *Hp* in the adult population in Turkey is 67.6%-81.3% (3, 4). *Hp* infection can also cause chronic active gastritis, gastric cancer and MALT (mucosa associated lymphoid tissue) lymphoma (5-9).

Eradication of *Hp* lowers the recurrence rate of pep-

Address for correspondence: Ali ÖZDEN
Kardelen Mh. 12. Cd. 317. Sk. No: 20
Kar-me, Batıkent, Ankara / Turkey

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tic ulcer (10). Eradication of *Hp* can be achieved with different types of regimens. Standard triple therapies containing a proton pump inhibitor (PPI) and two antibiotics are the most commonly used treatments for *Hp* eradication in clinical practice (11). However, recent studies from many countries have reported the failure of these regimens (12, 13). A national meta-analysis showed that the average *Hp* eradication rate with PPI-based triple regimens in Turkey had decreased from 84% in 1997 to 55.3% in 2004 (13). Clarithromycin resistance and patient noncompliance are cited as the most important causes of failure with these regimens (14, 15). Clarithromycin resistance has reached 50% in Turkey (16). Therefore, an increasing number of patients actually require a second or further therapeutic attempt to eradicate the infection. The sequential regimen is a novel, promising therapeutic approach for *Hp* eradication (17-19). We aimed to report herein the outcomes of different *Hp* eradication regimens used in our institution over the last 10 years.

METHODS

This retrospective study included the data of a total of 400 consecutive patients. The patients admitting to the Gastroenterology Department with dyspeptic complaints and *Hp* positivity between 1999 and 2009 and who were referred for endoscopic examination were included. Endoscopic biopsy was taken from the antrum and corpus for cytology, culture and rapid urease test.

Diagnosis of *Hp* infection

Hp infection was diagnosed by histopathological examination of antrum and corpus biopsy material obtained during endoscopy. Rapid urease test, *Hp* cytology and *Hp* culture (in-house) tests were performed as a diagnostic panel in all of the cases. *Hp* positivity was considered with at least two positive results among cytological, rapid urease and microbiological examinations.

Treatment Regimens

Patients received different *Hp* eradication protocols during the 10-year period. Treatment regimens according to groups were as follows: Group 1) PPI b.i.d., clarithromycin 500 mg b.i.d. and amoxicillin 1000 mg b.i.d. for 2 weeks; Group 2) Colloidal bismuth subcitrate 300 mg q.i.d., metronidazole 500 mg t.i.d. and tetracycline 500 mg t.i.d. for 2 weeks; Group 3) ranitidine bismuth citrate (RBC) 400 mg b.i.d., clarithromycin 500 mg b.i.d. and amoxicillin 1000 mg b.i.d. for 2 weeks; Group 4) PPI b.i.d., colloidal bismuth subcitrate 300 mg q.i.d., clarithromycin 500 mg b.i.d. and amoxicillin 1000 mg b.i.d. for 2 weeks; Group 5) PPI b.i.d., tetracycline 500 mg t.i.d. and amoxicillin 1000 mg b.i.d. for 2 weeks; and Group 6) a 14-day sequential regimen: PPI b.i.d. and amoxicillin 1000 mg b.i.d. for 5 days, followed consecutively by PPI b.i.d., clarithromycin 500 mg b.i.d. and metronidazole 500 mg b.i.d. for 5 days.

Test for *Hp* Eradication

Endoscopic biopsy, rapid urease test, *Hp* cytology and culture tests were repeated six weeks after the treatment. *Hp* eradication was accepted when all three tests were negative.

Statistics

The data were analyzed with SPSS for Windows version 11.0. T test and chi-square test were used where appropriate. A p value less than 0.05 was considered as statistically significant.

RESULTS

In our study, data of 400 patients were analyzed retrospectively. The study population included 221 female (53.2%) and 179 male (46.8%) patients with a mean age of 47.5 years. 324 (81%) patients were diagnosed with non-ulcer dyspepsia while 76 (19%) patients had duodenal ulcer disease.

Subjects were allocated into one of the six groups according to their treatment regimens as follows: Group 1 consisted of 169 (F/M: 82/87) patients with a mean age of 45.9±15.0 years; Group 2 consisted of 27 (F/M: 12/15) patients with a mean age of 49.0±13.5 years; Group 3 consisted of 97 (F/M: 73/24) patients with a mean age of 45.6±11.6 years; Group 4 consisted of 27 (F/M: 15/12) patients with a mean age of 45.8±11.2 years; Group 5 consisted of 68 (F/M: 33/35) patients with a mean age of 46.5±12.1 years; and Group 6 consisted of 12 (F/M: 6/6) patients with a mean age of 47.5±18.0 years.

Hp eradication rate was 74.7% (126/169) for Group 1, 92.3% (25/27) for Group 2, 81.2% (79/97) for Group 3, 81.5% (22/27) for Group 4, 70.5% (48/68) for Group 5, and 66.6% (8/12) for Group 6. Treatment was not discontinued in any of the patients due to side effects. None of the subjects forgot to take the medications or changed their order. *Hp* treatment regimens and eradication rates are summarized in Table 1.

DISCUSSION

The ultimate goal of the *Hp* eradication therapy,

obviously, is the effective elimination of the infection in all treated patients. The eradication regimens achieving over 80% eradication rates with intention-to-treat (ITT) analysis were recommended in consensus reports (20, 21). In primary health care service, the most commonly used regimen is PPI (lansoprazole 30 mg b.i.d., omeprazole 20 mg b.i.d. or pantoprazole 40 mg b.i.d.), amoxicillin 1000 mg b.i.d. and clarithromycin 500 mg b.i.d. for 7 to 14 days, but with only a 5% increase in eradication rates in recent years (22). Published studies and meta-analyses have shown that classical triple therapies were 20% less successful than expected. Additionally, in recent years, researchers have increasingly concluded that due to the increase in antibiotic resistance, eradication rates of classical triple regimens have decreased.

In one study, resistance to clarithromycin and metronidazole was seen in 16.9% and 29.4% of patients, respectively (23). In our country, Cirak et al. reported that the resistance to both metronidazole and clarithromycin among subjects had increased to 50% (16). In this study, the classical triple regimen eradication rate was found as 74.7%. However, in our first study in 1998, we applied the treatment with the triple regimen including clarithromycin for two weeks and the eradication rate was determined as 90% (from February 1995 to March 1996, patients treated with triple regimen – PPI, clarithromycin and amoxicillin) (24). Especially in recent years, the decrease in the eradication rate is likely to be associated with an increase in clarithromycin resistance.

In the published studies, it was reported that resistance to metronidazole and clarithromycin was frequently encountered, while tetracycline and amoxicillin resistance was rare (25). In our study, tetracycline 500 mg t.i.d., amoxicillin 1000 mg b.i.d. and PPI b.i.d. as a two-week course achieved a 70.5% eradication rate. This result was similar to that achieved with the classical triple *Hp* eradication regimen.

In vitro studies suggest a synergistic activity between RBC and clarithromycin. Osato et al. had shown a synergy between RBC and clarithromycin with a decrease of RBC minimal inhibitory concentrations (MICs) from more than 8 mg/L to less than 2 mg/L in 8 of 10 clarithromycin-resistant *Hp* strains (26). RBC can release bismuth, which has also been shown to have moderate anti-*Hp* activity in the gastric mucosa (27). The level of bismuth concentration achieved in the mucosa is very important and markedly higher than the MIC. PPIs have anti-*Hp* activity at high concentrations, which are unlikely to be achieved in vivo (28). When used together with a PPI, anti-*Hp* activity of clarithromycin is mostly due to an elevated pH, which decreases the MIC of clarithromycin, and possibly leads to decreased volume of secretion, which may in turn increase the clarithromycin concentration (29, 30). Furthermore, in vivo studies support this condition.

Table 1. *Helicobacter pylori* treatment regimens and eradication rates

Group	Patient number (n)	Treatment Regimen	Treatment Duration (week)	Eradication Rate (%)
1	169	• PPI b.i.d. • Clarithromycin 500 mg b.i.d. • Amoxicillin 1000 mg b.i.d.	2 weeks	74.7
2	27	• Colloidal bismuth subcitrate 300 mg q.i.d. • Metronidazole 500 mg t.i.d. • Tetracycline 500 mg t.i.d.	2 weeks	92.3
3	97	• Ranitidine bismuth citrate 400 mg b.i.d. • Clarithromycin 500 mg b.i.d. • Amoxicillin 1000 mg b.i.d.	2 weeks	81.2
4	27	• PPI b.i.d. • Colloidal bismuth subcitrate 300 mg q.i.d. • Clarithromycin 500 mg b.i.d. • Amoxicillin 1000 mg b.i.d.	2 weeks	81.5
5	68	• PPI b.i.d. • Tetracycline 500 mg t.i.d. • Amoxicillin 1000 mg b.i.d.	2 weeks	70.5
6	12	• PPI b.i.d. • Amoxicillin 1000 mg b.i.d. • Clarithromycin 500 mg b.i.d. • Metronidazole 500 mg b.i.d.	PPI + A 5 days PPI + C + M 5 days	66.6

Megraud et al. had reported eradication rates of 33% and 92% in clarithromycin-resistant patients with omeprazole-clarithromycin and RBC-clarithromycin dual therapies, respectively (31). Houben et al. had reported that in the case of clarithromycin resistance, a mean drop in efficacy of 56% was found for clarithromycin-containing PPI-triple therapies, while in contrast, for RBC combined with clarithromycin and nitroimidazole, no difference in efficacy was found with respect to clarithromycin resistance (32). In a study of Bago et al., *Hp* eradication rates in clarithromycin-resistant patients were found to be 40% and 80% with omeprazole - amoxicillin - clarithromycin and RBC - amoxicillin - clarithromycin therapies, respectively (33). In our study, we used three different *Hp* eradication treatment protocols as colloidal bismuth subcitrate – metronidazole - tetracycline, RBC - clarithromycin - amoxicillin and colloidal bismuth subcitrate - clarithromycin - amoxicillin – PPI, and *Hp* eradication results were found as 92.3%, 81.2% and 81.5%, respectively. In our country, RBC - amoxicillin - clarithromycin triple regimen as performed by Avşar et al., Hatemi et al., Alkım et al., and Cınar et al. documented *Hp* eradication rates of 74.6%, 76.7%, 87%, and 95.9%, respectively (34-37). In another study, Aydın et al. had reported that treatment with RBC - amoxicillin - clarithromycin resulted in an eradication rate of 80% in clarithromycin-resistant patients (38).

The currently recommended first-line treatments for *Hp* infection fail in a significant proportion of patients for several reasons, including bacterial resistance, poor compliance, treatment-related factors including the number and doses of medications used in combination, dosing frequency, treatment duration, and patient-related factors (15, 39). As a result, there has been intensive search for highly effective new first- and second-line therapies.

Sequential treatment was proposed as an effective regimen in clarithromycin-resistant *Hp* strains (40). Uygun et al. modified the sequential treatment and treated naive subjects with a sequential regimen containing pantoprazole 40 mg b.i.d. and amoxicillin 1 g b.i.d. for 7 days, followed by pantoprazole 40 mg b.i.d., tetracycline 500 mg q.i.d., and metronidazole 500 mg b.i.d. for the next 7 days. In that trial, the eradication rates were 72.6% for ITT analysis and 80.1% for per-protocol (PP) analysis (41). However, with a similar regimen, Sezgin et al. reported unacceptably low eradication rates, i.e., ITT 50% and PP 57% (42). In another study, Aydin et al. evaluated the effectiveness of levofloxacin-based sequential treatment in *Hp* eradication in 63 treatment-naive patients and 37 previous treatment failures. In treatment-naive patients, ITT and PP eradication rates were 82.5% and 86.7%, respectively. As a second-line treatment, eradication was successful, with ITT 75.7% and PP 80% (19). In the case of clarithromycin resistance, it was suggested that consecutive therapies comprising three antibiotics can increase the eradication rate (43-46). In the treatment arm beginning with amoxicillin 1000 mg b.i.d. and PPI b.i.d. for 5 days and continuing with a 5-day course of clarithromycin 500 mg b.i.d., metronidazole 500 mg t.i.d. and PPI b.i.d., the eradication rate was 66.6%. In this treatment group, the number of cases was small, so it would be judicious to repeat this analysis with a larger number of cases.

In conclusion, we have reported our results with different treatment regimens in *Hp* eradication over the last 10 years. The highest eradication rate was in the colloidal bismuth subcitrate - metronidazole - tetracycline combination group, with a rate of 92.3%. The consecutive regimen failed to achieve the recommended eradication rates.

Because of the common use of clarithromycin worldwide, clarithromycin resistance is increasing. Thus, clarithromycin should not be included in the triple treatment protocol. Especially in those countries with very high resistance to clarithromycin, like Turkey, we suggest a triple treatment regimen including bismuth subcitrate or tetracycline, amoxicillin, metronidazole and PPI.

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