Turk J Gastroenterol 2010; 21 (3): 206-211

Sequential therapy for *Helicobacter pylori* eradication

Helikobakter pilori eradikasyonunda ardışık tedavi

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Background and aims: *The success of Helicobacter pylori eradication using triple eradication therapy declines over time. In this prospective study, we have compared a group of naive H. pylori-positive patients receiving sequential therapy with our previously published naive H. pylori-positive control group who received ranitidine bismuth citrate -clarithromycin-amoxicillin eradication treatment. Moreover, the eradication success of these two treatment protocols was compared with that of recent standard triple eradication treatment results for the naive patients in our country and western communities.* ***Methods:*** *We performed invasive tests for H. pylori in naive patients who underwent gastroduodenoscopy in the Endoscopy Unit, Ankara University, Faculty of Medicine, and patients who were diagnosed as H. pylori-positive by these tests were rechecked by the same invasive tests one month after the completion of eradication treatment. The group receiving sequential therapy was given pantoprazole + amoxicillin during the first seven days and pantoprazole + metronidazole + tetracycline during the second seven days. These patients were compared with the H. pylori-positive naive control group patients, who were given ranitidine bismuth citrate+ clarithromycin + amoxicillin. The patients in whom eradication was achieved in the 4th week with sequential therapy were reevaluated one year later regarding the success of eradication with the H. pylori stool antigen test.* ***Results:*** *The average age of the 108 patients who received the sequential therapy was 45.2±12.5 years. The average age of the 75 patients who received ranitidine bismuth citrate treatment was 41.2±12.6 years. Six (5%) patients in the consecutive treatment group developed deterioration in taste in the mouth and 10 (9%) developed diarrhea. However, no side effects severe enough to require discontinuation of the treatments were observed in either treatment group. The results of the invasive tests were evaluated by the end of the first month, and revealed an eradication rate of 88% in the sequential treatment group versus 95% in the ranitidine bismuth citrate treatment group. Sixty-eight of 94 patients in whom eradication was achieved by sequential therapy were reevaluated with H. pylori stool antigen test in one year, and eradication was found to persist in 52 (77%) of these 68 patients.* ***Conclusions:*** *High rates of eradication were achieved in both groups in the 4th week evaluation. It was observed at the follow-up performed one year later that the eradication achieved with sequential therapy persisted in 77% of the patients treated.*

Key words: Sequential therapy, ranitidine bismuth citrate, eradication, *H. pylori*

Amaç: *Helikobakter pilori tedavisinde kullanılan üçlü eradikasyon tedavisinin başarı oranları zamanla düşmektedir. Bu prospektif çalışmada naif Helikobakter pilori pozitif hastalara ardışık tedavi verildi ve bu hastalar daha önce yayınladığımız naif Helikobakter pilori pozitif ranitidin bizmut sitrat+klaritromisin+amoksisilin tedavisi alan grup ile karşılaştırıldı. Ayrıca bu iki tedavi protokolu sonuçları ülkemiz ve batı ülkeleriden yayınlanan üçlü eradikasyon tedavisinin başarı oranları ile karşılaştırıldı.* ***Metod:*** *Ankara Üniversitesi Tıp Fakültesi Gastroenteroloji Ünitesi Endoskopi Ünitesinde gastroduodenoskopi yapılarak invazif testler ile Helikobakter pilori saptanan ve tedavi edilen hastalar bir ay sonra yine invazif testler ile Helikobakter pilori için kontrol edildi. Ardışık tedavi alan gruba ilk 7 gün pantoprazol ve amoksisilin tedavisi, ikinci 7 gün pantoprazol-tetrasiklin-metronidazol tedavisi verildi. Ardışık tedavi ile eradikasyon sağlanan hastalarda bir yıl sonra dışkıda Helikobakter pilori antijen testi ile eradikasyon başarısı kontrol edildi.* ***Bulgular:*** *108 ardışık tedavi alan hastanın ortalama yaşı 45.2±12.5 yaş idi. Ranitidin bizmut sitrat+klaritromisin+amoksisilin tedavisi alan 75 hastanın yaş ortalaması 41.2±12.6 idi. Ardışık tedavi alan 6 hastada ağız tadında bozukluk, 10 hastada diare şikayetleri oldu. Her iki grubta da yan etki nedeni ile tedaviyi bırakan olmadı. Birinci ay sonu değerlendirmede ardışık tedavi alan grupta %88, ranitidin bizmut sitrat+klaritromisin+amoksisilin tedavisi alan grupta %95 eradikasyon sağlandı. Ardışık tedavi ile eradikasyon sağlanan 94 hastadan 68 hasta bir yıl sonra dışkıda Helikobakter pilori antijen testi ile tekrar değerlendirildi. Bu 68 hastanın 52 (%77)sinde eradikasyon devam ediyordu.* ***Sonuç:*** *Her iki grupta da dördüncü hafta değerlendirmesinde yüksek eradikasyon oranları saptandı. Bir yıl sonraki değerlendirmede ardışık tedavi ile eradikasyon sağlananların %77'sinde eradikasyonun devam ettiği izlendi.*

Anahtar kelimeler: Ardışık tedavi, ranitidine bismuth sitrat, eradikasyon, *Helikobakter pilori*

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Manuscript received: 08.06.2009 **Accepted:** 01.10.2009

doi: 10.4318/tjg.2010.0089

INTRODUCTION

Helicobacter pylori (H. pylori) is one of the most common infectious diseases in the world (2). The Maastricht consensus group recommends eradication of *H. pylori* in many clinical cases. *H. pylori* also plays a role in gastric carcinogenesis (3). For these reasons, many treatment protocols have been attempted for the eradication of *H. pylori*. The triple eradication protocol of clarithromycin, amoxicillin, and proton pump inhibitor (PPI) combination is the most frequently used in our country and western communities. If the success rates are less than 80% in the *H. pylori* eradication treatment, the eradication rates are considered insufficient (4). Since the desired success rates are not achieved using the triple treatment protocol, alternative treatment protocols are attempted on naive patients.

It has been observed in the recent triple combination studies in western communities and our country that the eradication success declines over time (5,6). In recent studies, it was reported that clarithromycin resistance is the reason for failure in one-third of the cases in which eradication is not achieved using the standard triple treatment (7). Very successful eradication rates in naive patients and resistant cases have been reported using sequential treatment and ranitidine bismuth citrate (RBC) protocols (6).

In this study, we compared the demographic properties and eradication success results of 108 naive *H. pylori*-positive patients who received sequential treatment with the results of our previously reported (1) 75 naive *H. pylori*-positive patients who received RBC-clarithromycin-amoxicillin eradication treatment. Moreover, the eradication rates of these two treatment groups were compared with the recent results of standard triple eradication treatment of naive patients in our country and western communities. Since high eradication success rates are achieved using both of the treatment protocols, it is a logical choice to use these two *H. pylori* eradication protocols on naive patients in countries like Turkey, in which *H. pylori* prevalence and clarithromycin resistance are high and eradication success rates with the triple treatment protocols are low.

MATERIALS AND METHODS

Patients

Gastroduodenoscopy was applied to patients between September 2008 and April 2009 in the Endoscopy Unit, Ankara University, School of Medicine, and 108 of these patients were diagnosed as *H. pylori*-positive using invasive tests; these patients were prospectively considered for eradication treatment success. The control was performed using our published results in 2004 for 75 patients who were diagnosed as naive *H. pylori*-positive by invasive tests and were treated with RBC-clarithromycin-amoxicillin eradication therapy. Among 94 patients in whom eradication was established in the 4-week post-treatment assessment, the presence of *H. pylori* was reevaluated in 68 patients who presented for a follow-up visit at the end of one year.

Diagnosis of *H. pylori* and Evaluation of Treatment Success

Two biopsies were taken from the antral prepyloric regions of all patients by endoscopic examination. At the first examination, *H. pylori* was investigated using histopathological analysis, CLO test, *H. pylori* cytology, and *H. pylori* culture methods. The patients who were diagnosed as *H. pylori*- positive after these invasive tests and who received eradication treatment were followed up after a month. At the follow-up endoscopic examination, biopsies were taken from the antrum and *H. pylori* presence was investigated using *H. pylori* culture, *H. pylori* cytology and CLO test. *H. pylori* stool antigen test was used at the evaluation performed after one year.

Treatment Protocol

The patients were given pantoprazole 40 mg bid + amoxicillin 1 g bid treatment for the first 7 days, and pantoprazole 40 mg bid + metronidazole 500 mg bid + tetracycline 500 mg bid treatment for the second 7 days. The control group patients had been given 400 mg/day RBC + 500 mg/day clarithromycin + 2000 mg/day amoxicillin treatment.

Statistical Analysis

The data were examined using SPSS 15.0 computer software. Statistical analyses were performed using T-test and chi-square test. A p value less than 0.05 was considered statistically significant.

RESULTS

Demographic properties, *H. pylori* diagnostic methods, and eradication rates for 108 naive *H. pylori*-positive patients who received sequential eradication therapy were compared with those of 75 naive *H. pylori*-positive patients who received

RBC-clarithromycin-amoxicillin eradication therapy. All 108 patients who received sequential therapy had applied to our clinic with complaints of dyspepsia. Gastroduodenoscopic examination of these 108 patients revealed superficial antral gastritis in 94 patients, mamillary antral gastritis in 5 patients, pangastritis in 5 patients, atrophic gastritis in 2 patients, duodenal ulcer in 1 patient, and gastric ulcer in 1 patient.

For all patients in the RBC-clarithromycin-amoxicillin group, *H. pylori* assessment was performed using a combination of histopathological examination, *H. pylori* culture, *H. pylori* cytology, CLO test, urea breath test, and stool *H. pylori* antigen methods at the beginning and the end of the first month. For the sequential therapy group, the initial *H. pylori* assessment was performed using histopathological assessment in 23/108 (21%) patients and a combination of *H. pylori* culture, *H. pylori* cytology and CLO test in 85/108 (79%) patients. By the end of the first month, *H. pylori* control was performed using a combination of *H. pylori* culture, *H. pylori* cytology and CLO test in all patients in the sequential therapy group. *H. pylori* culture, *H. pylori* cytology and CLO tests used at the beginning and at the follow-up in the sequential therapy group were 100% compatible.

The average age of the group receiving the RBC-clarithromycin-amoxicillin treatment was 41.2±12.6 (range: 16-72 years), and 49 (65.3%) were women and 26 (34.6%) were men. The average age of the group receiving the sequential treatment was 45.2±12.5 (range: 19-76 years), and 64 (59.2%) of these patients were women and 44 (40.7%) were men. There was no significant difference between the two groups in terms of age and gender distribution ($p>0.05$). In the sequential treatment group, 6 (5%) patients reported deterioration in taste in the mouth and 10 (9%) developed diarrhea. However, no side effects severe enough to result in discontinuation of the treatment were observed in either treatment group. The eradication rate for the first group receiving the sequential treatment was 88% (95/108), according to the follow-up assessment performed at the end of the first month. The eradication rate for the group receiving the RBC treatment was 95% (72/75) according to the follow-up assessment at the end of the first month. The eradication rate was higher in the RBC-clarithromycin-amoxicillin treatment group; however, there was no statistically significant difference between the two treatment groups in terms of eradication success ($p=0.058$).

Of the 94 patients in whom eradication was achieved at the end of first month with sequential therapy, the eradication rates were reevaluated in 68 patients by *H. pylori* stool antigen test at the end of one year. Eradication persisted in 52 of the 68 patients reevaluated at the end of one year, and *H. pylori* had become positive again in 16 patients.

DISCUSSION

Helicobacter pylori is one of the most common infectious diseases observed worldwide (2). Studies show that *H. pylori* spread from East Africa approximately 58 thousand years ago by human migration (6). It generally settles at the antrum, though frequently at the corpus as well. The diagnostic tests for *H. pylori* (and their sensitivity and specificity, respectively) are histopathological examination (80% and 100%), *H. pylori* culture (90% and 100%) and cytological examination (98% and 100%) (8). We used these invasive tests, which individually are very sensitive in the diagnosis and control of *H. pylori*, in combination in both treatment groups at the 4th week assessment in our study. However, for the assessment performed at the end of the first year after consecutive treatment, we used the *H. pylori* stool antigen test, which is considerably specific and sensitive.

A significant change has occurred in the treatment of upper gastrointestinal diseases with the discovery of *H. pylori* by Warren and Marshall (6). *H. pylori* eradication therapy is recommended in many clinical situations. Moreover, the Maastricht consensus group has recognized the relationship between *H. pylori* and gastric cancer and recommended additional studies in this area (3). Since the eradication of *H. pylori* for several aforementioned clinical cases is recommended and it is known that *H. pylori* plays a role in gastric carcinogenesis, success rates of eradication protocols have become important and many eradication protocols have been tested.

Triple eradication therapy is the most commonly used treatment protocol in *H. pylori* eradication (6). Laine achieved a 75% success rate in a 10-day treatment study in 1998, whereas Fennerty achieved an 81% eradication success rate in a 10-day treatment study in the same year using the triple eradication therapy (6). It has been observed in recent studies performed with triple combination in western countries that the eradication success rates have been declining over the years. Bochenek et al. (9) achieved a 57%-73% success rate in a 7-

day study, whereas Vakil et al. (6) achieved a 67%-79% eradication success rate in a 10-day treatment study. Our country is similar to the developing countries in terms of *H. pylori* prevalence. In a study published in 2003 in Turkey, 3584 patients were evaluated and *H. pylori* frequency was reported as 83% (5). PPI bid, clarithromycin 500 mg bid and amoxicillin 1 g bid treatment regimen was used for 7 or 14 days on 2763 patients between 1996-2003, and the eradication rate was found as 73.1% in the meta analyses. The eradication rate was 84% after a 14-day triple therapy in 1996, while it was reported as 59% in 2002 and 65% in 2003. Moreover, for 1098 patients who received the triple therapy for 14 days between 2000 and 2003, the eradication rate was reported as 62% (5). The eradication success rates have been declining over the years in Turkey as well, in parallel with the world literature.

In the studies performed in recent years, clarithromycin resistance is reported as the reason for failure in one-third of the cases in which the eradication was not successful using the standard triple therapy (7). Therefore, when the failed cases are treated for a second time, the eradication treatment options should not include clarithromycin. Since amoxicillin resistance is rare, the eradication regimen should continue with amoxicillin. In an evaluation performed in the United States using the data from 1999-2000, clarithromycin resistance was determined as 10-12%. In a study performed in Europe in 17 centers, clarithromycin resistance was determined as 1-3% in the northern countries, 12.6% in the central European countries and 20% in the southern countries (10). The rates of secondary resistance to clarithromycin have been reported as 42% in Europe and 67% in Israel. Clarithromycin resistance rates have been reported to be as high as 10-20% in our country (11-13).

For the cases in which *H. pylori* eradication can not be achieved using the triple therapy, treatment regimens like bismuth-PPI-tetracycline-metronidazole sequential eradication therapy and salvage therapy (by adding levofloxacin 500 mg/day, rifabutin 300 mg/day or furazolidone 200-400 mg/day to PPI bid + amoxicillin 1 g bid treatment for 10 days) are recommended (6). Since *H. pylori* eradication rates with PPI, amoxicillin, and clarithromycin triple therapy have been dropping throughout the world and especially in our country and since clarithromycin resistance has been reported to be high in recent studies, use of the above-mentioned treatment protocols has become more widespread in naive patients as well.

Bismuth reduces antibiotic resistance (14) and its use is an effective treatment strategy in *H. pylori* eradication in those regions where clarithromycin resistance is high. In a wide series of studies, a 78% eradication rate was achieved with bismuth + metronidazole + tetracycline triple treatment, while an 82% eradication rate was achieved with bismuth + metronidazole + tetracycline + PPI (6,15). RBC + clarithromycin + amoxicillin combination is reported to be effective in *H. pylori* treatment. In one study, 83% eradication was achieved with this combination (16). In the RBC-clarithromycin-amoxicillin group of our study, we treated 75 patients and achieved a 95% eradication rate.

It has been observed during the sequential treatment periods using amoxicillin + PPI treatment that more successful results are achieved when this double treatment is followed by a 7-day triple therapy. It is predicted that since a low-resistance antibiotic, such as amoxicillin, reduces the concentration of bacteria in the stomach, the effect of the sequentially administered second antibiotic is increased (6). Studies with sequential treatment were generally performed using PPI + amoxicillin 1 g during the first 5 days and PPI + clarithromycin 500 mg or tinidazole 500 mg (twice a day) during the second 5-day treatment scheme (6). Very successful eradication rates were reported with this sequential treatment scheme. Particularly in studies in Italy (including a total of more than 1000 patients), eradication rates were reported to be more than 90% [92% in 522 patients, Zullo et al. (17), 93.4% in 152 patients, Hassan et al. (18), 95% in 174 patients, Focareta et al. (19), 93% in 162 patients, De Francesco et al. (20), and 91% in 146 patients, Vaira et al. (21)]. Due to the high incidence of clarithromycin resistance in Turkey, we preferred metronidazole and tetracycline instead of clarithromycin in our sequential treatment protocol. Although a low eradication rate had been reported in a study (22) using PPI-amoxicillin-metronidazole-tetracycline sequential protocol with 32 patients, Uygun et al. (23) reported an eradication rate of 80.1% in a study with 150 patients. At the post-treatment 4th week evaluation of the sequential treatment group using PPI-amoxicillin-metronidazole-clarithromycin, we achieved an 88% eradication rate in our study.

In addition to the drug resistance, the other factors responsible for the failure in *H. pylori* eradication therapy are the side effects linked to antibiotics (6). In a study performed in France with 2751 patients, diarrhea (8%), taste changes in mouth (7%), nausea and vomiting (5%), skin rashes (2%), headache (4%), abdominal discomfort (5%), and stomatitis (2.5%) were reported as related with eradication treatments (24). In our study, taste changes in the mouth in 6 (5%) patients and diarrhea complaint in 10 (9%) patients were observed in the sequential therapy group. However, no side effect necessitating discontinuation of the treatment was observed in either group.

Sixty-eight out of 94 (88%) patients in whom eradication was achieved in the 4th week with sequential treatment were reevaluated one year later regarding the success of eradication, using the *H. pylori* stool antigen test. At the one-year evaluation, 16 of these 68 patients were found to be *H. pylori*-positive again. This finding may have been due to a false-positive result with the invasive tests used in the 4th week evaluation, an antral biopsy obtained from a location lacking *H. pylori* colonization, a false-negative *H. pylori* test result due to the acid suppressant effect of pantoprazole treatment, and, though less likely, reinfection (25-27).

In conclusion, the eradication success using the triple therapy has been declining over the years, and clarithromycin resistance is the most common reason for the treatment failure. In this study, the success rates in both the sequential and RBC-clarithromycin-amoxicillin therapy groups were higher than the recent triple therapy eradication rates reported in our country and western countries. According to the post-treatment 4th week assessment, the success rate was higher in the RBC-clarithromycin-amoxicillin therapy group than the sequential therapy group; however, the difference was not statistically significant (95% (72/75) vs 88% (95/108); p=0.058). Among the patients in whom eradication was achieved with sequential treatment, it was observed to persist in 77% of patients at the one-year assessment.

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