Original Article
Sequential therapy versus standard triple therapy in Helicobacter pylori eradication in a high clarithromycin resistance setting

Can Dolapcioglu[1], Aysun Koc-Yesiltoprak[2], Emel Ahishali[1], Aziz Kural[1], Hatice Dolapcioglu[3], Aliye Soylu[4], Resat Dabak[2]

[1]Department of Gastroenterology, Dr. Lutfi Kirdar Kartal Research and Training Hospital, Kartal, Istanbul, Turkey;
[2]Department of Family Medicine, Dr. Lutfi Kirdar Kartal Research and Training Hospital, Kartal, Istanbul, Turkey;
[3]Department of Pathology, Fatih Sultan Mehmet Research and Training Hospital, Istanbul, Turkey; [4]Department of Gastroenterology, Dr. Sadi Konuk Bakirkoy Research and Training Hospital, Bakirkoy, Istanbul, Turkey

Abstract: Sequential treatment scheme has been developed to overcome resistance problem in H. pylori eradication and favorable results have been obtained. This study compared the results of standard triple therapy with a sequential schema consisting of pantoprazole, amoxicillin, clarithromycin, and metronidazole in a high anti-microbial resistance setting. This retrospective study included subjects that underwent standard or sequential eradication treatment after a diagnosis of biopsy-documented H. pylori infection. Patients either received pantoprazole 40 mg bid, amoxicillin 1000 mg bid and clarithromycin 500 mg bid (PAC) for 10 days, or pantoprazole 40 mg bid and amoxicillin 1000 mg bid (PA) for the first 5 days of the treatment period and were then given pantoprazole 40 mg bid, clarithromycin 500 mg bid, and metronidazole 500 mg bid (PCM) in the remaining 5 days. Eradication was tested using urea breath test. The two treatment groups did not differ with regard to H. pylori eradication rate for both ITT population (63.9% versus 71.4% for standard and sequential therapy respectively, $P = 0.278$) and per protocol population (65.9% versus 74.1% for standard and sequential therapy respectively, $P = 0.248$). Although a sequential treatment appears to represent a plausible alternative, our findings suggest that alternative schedules may be required in certain populations to achieve higher success rates.

Keywords: H. pylori, standard therapy, sequential therapy, eradication

Introduction

Despite high prevalence rates of Helicobacter pylori (H. pylori) infection across populations reaching 50%, this common infection can generally be successfully treated [1]. Human gastric colonization of H. pylori has been associated with a wide spectrum of gastroduodenal disorders ranging from dyspepsia, chronic gastritis, acute atrophic gastritis and peptic ulceration to MALT lymphoma and gastric carcinomas [2]. Also, inconclusive evidence suggests a link between H. pylori and several extra-gastric conditions such as cardiovascular or neurological diseases [1, 3].

Eradication of H. pylori infection with anti-microbial agents is an effective method to treat or prevent a number of different gastrointestinal conditions as well as for the reduction of cancer risk [4]. Although a variety of anti-microbial combinations have been used for the eradication of H. pylori, the first-line treatment in Europe and North America comprises amoxicillin and clarithromycin combined with PPIs. This also represents the most widely prescribed regimen in Turkey. However, eradication rates with PPI, amoxicillin and clarithromycin combination have been continuously declining, with reported success rates of 50 to 60% in Turkish patient populations [5]. The foremost factor responsible for the decreased rates of H. pylori eradication is the resistance to clarithromycin and metronidazole, and the reported resistance rates among H. pylori strains for the former anti-microbial agent is 38.5% in Turkey [5].

Table 1. Baseline characteristics of the treatment groups (ITT population)

Characteristic	Standard triple therapy n = 91	Sequential therapy n = 84	P value
Age, y (mean ± SD)	43.6 ± 12.8	41.9 ± 10.5	0.338
Female gender	49 (53.8%)	45 (53.6%)	0.971
Presence of comorbid conditions	29 (31.9%)	34 (40.5%)	0.236
Smoking	21 (23.1%)	25 (29.8%)	0.316
Endoscopic findings			
Gastritis	67 (77.0%)	58 (69.0%)	0.240
Duodenal ulcer	14 (16.1%)	19 (22.6%)	0.280
Gastric ulcer	6 (6.9%)	5 (6.0%)	0.801
Metaplasia	14 (15.4%)	16 (19.0%)	0.521

Data are presented as n (%) unless otherwise stated.

Table 2. Treatment success and side effects of the two treatments (ITT and per protocol populations)

ITT population n = 175	Standard triple therapy n = 91	Sequential therapy n = 84	P value
Eradication	58 (63.9%)	60 (71.4%)	0.278
Symptoms after treatment	30 (33.0%)	22 (26.2%)	0.327
Presence of treatment side effect	26 (28.6%)	26 (31.0%)	0.731
Per protocol population n = 196	Standard triple therapy n = 88	Sequential therapy n = 81	P value
Eradication	58 (65.9%)	60 (74.1%)	0.248
Symptoms after treatment	29 (33.0%)	21 (25.9%)	0.317
Presence of treatment side effect	23 (26.1%)	23 (28.4%)	0.742

Data are presented as n (%).

Sequential treatment scheme developed to circumvent the resistance problem [6] involves the use of multiple antibiotics according to a certain time-schedule with positive results reported in various patient populations [7-9].

In the present study, the standard triple treatment consisting of PPI, amoxicillin and clarithromycin was compared with sequential treatment involving a PPI, amoxicillin, clarithromycin, and metronidazole with regard to their ability to eradicate H. pylori in a population with established high anti-microbial resistance.

Material and methods

Subjects

A retrospective examination of the medical records of patients attending to our unit between January and July 2012 with gastric complaints was performed and subjects undergoing standard or sequential eradication treat-

ment after a diagnosis of biopsy-documented H. pylori infection were included in the study. Patients in the standard treatment group received pantoprazole 40 mg bid, amoxicillin 1000 mg bid and clarithromycin 500 mg bid (PAC) for 10 days, while those in the sequential treatment group received pantoprazole 40 mg bid and amoxicillin 1000 mg bid (PA) for the first 5 days of the treatment period and were then given pantoprazole 40 mg bid, clarithromycin 500 mg bid, and metronidazole 500 mg bid (PCM) in the remaining 5 days. Patients in both groups continued pantoprazole 40 mg qd for one month after the completion of eradication therapy and urea-breath test was used to assess the success of the treatment 4 weeks after the completion of treatment. Patients without a pathology and patients without a urea-breath test result were not included.

Statistical analyses

Data analysis was performed using SPSS v21.0 statistical software package. Intergroup comparisons of categorical variables were done using Pearson Chi-square test and continuous variables were compared using student t test for independent samples. In order to identify the independent predictors of H. pylori eradication, stepwise logistic regression was used. A *P* value smaller than 0.05 were considered an indication for statistical significance.

Results

Treatment groups

A total of 175 patients were included in the intention-to-treat (ITT) population: standard triple therapy group, n = 91; sequential therapy group, n = 84. **Table 1** shows baseline characteristics of the two treatment groups. Groups did not differ with regard to demographical and clinical characteristics. Six patients were non-compliant to treatment protocol, thus per proto-

col population consisted of 169 patients: standard triple therapy group, n = 88; sequential therapy group, n = 81.

Treatment success

Table 2 shows treatment success and side effects of the two treatments for ITT and per protocol populations. The two treatment groups did not differ with regard to H. pylori eradication rate for both ITT population (63.9% versus 71.4% for standard and sequential therapy respectively, *P* = 0.278) and per protocol population (65.9% versus 74.1% for standard and sequential therapy respectively, *P* = 0.248). In addition, groups did not differ with regard to the rate of treatment side effects and persistent dyspeptic symptoms after treatment, for both ITT and per protocol populations. Most frequent side effects in the ITT population were diarrhea (13.7%), metallic taste (9.1%), nausea/vomiting (4.6%), and oral aphthous lesions (2.3%).

Predictors of eradication

In univariate analysis, presence of gastric ulcer was associated with a higher rate of eradication (35% vs. 0%, *P* = 0.017) but presence of gastritis was associated with a lower rate success (17% vs. 38%, *P* = 0.009). Multivariate analysis identified only the presence of gastritis as an independent predictor of eradication: OR, 2.96, (95% CI, 1.27-6.88), *P* = 0.012.

Discussion

Several factors have been associated with failure of first-line H. pylori eradication treatment including the bacterial resistance, number and dosage of medications in a given combination, duration of treatment, and patient-related factors [10]. However, the principal factor responsible for increased rates of treatment failure is clarithromycin and metronidazole resistance. It has been postulated that widespread prescription of macrolide antibiotics, particularly for the treatment of respiratory infections, might play a role in the development of clarithromycin resistance.

Although several authors proposed longer treatment courses for the triple therapy to enhance the therapeutic efficacy of this regimen, this approach is associated with increased treatment costs and may lead to reduced com-

pliance rates among patients. An alternative strategy involves the sequential use of different treatment schemes. In an earlier application of sequential treatment strategy, De Francesco was able to achieve a high eradication rate of 97% [11].

Current sequential treatments generally involve a two-drug regimen for the initial 5 day period, subsequently followed by the use of more than 2 antibiotics for a certain duration of time. Several studies have suggested higher eradication rates with this novel approach as compared to the standard treatment in different populations including children, adults, and the elderly [12].

In a Chinese study [12], a total of 215 H. pylori-positive patients were selected from 15,322 patients undergoing gastroscopy, for the comparison of the following three different treatment regimens: 10-day bismuth pectin quadruple therapy (20 mg of rabeprazole, 1000 mg of amoxicillin, 100 mg of bismuth pectin, and 500 mg of levofloxacin); sequential therapy (20 mg of omeprazole and 1000 mg of amoxicilline for 5 days followed by 20 mg of omeprazole, 500 mg of tinidazole and 500 mg of clarithromycin for the remaining 5 days); and standard 1-week triple therapy (20 mg of omeprazole, 1000 mg of amoxicillin, and 500 mg of clarithromycin). All three treatments were well tolerated, while sequential therapy achieved higher eradication rates in comparison with the standard therapy and bismuth pectin quadruple-therapy.

To date, a number of studies have tested sequential treatment against standard triple PPI based study with varying results. Chung et al. compared 10-day sequential therapy with 10-day triple therapy in a Korean population and found higher eradication rates with sequential therapy (ITT, 75.9% vs. 58.5%, PP, 86.8% vs. 67.6%), although the overall eradication rate was low [13]. The study by Chung et al. used a similar protocol with this study, except that lansoprazole was used instead of pantoprazole; and their population had high resistance rates for clarithromycin (18%) and metronidazole (41%). Authors explained the low overall eradication rate with high drug resistance and emphasized the need for more effective regiments. Tsay et al. compared a 7-day standard triple therapy with a 10-day sequential therapy, where both protocols used panto-

prazole similar to the present study [14]. In that Taiwan population, sequential therapy resulted in better and quite high eradication rates (93% vs. 80%) when compared to the standard therapy, with similar adverse event rates and drug compliance. Multivariate analysis identified sequential therapy as an independent factor predicting treatment success (OR, 1.23, 95% CI, 1.02-1.48). Two studies [15, 16] compared 7-day standard therapy with 10-day sequential therapy and both achieved better eradication rates with sequential therapy. The sequential regimen was better tolerated in the study by Lahbabi [16], whereas the two regimens were equally tolerated in the other study [15]. Liou et al. [17] examined the eradications rates of 3 regimens: 10-day and 14-day sequential therapies, and 14-day standard therapy. They obtained better eradication rates with 14-day sequential therapy when compared to the other two regimens, indicating the importance of the duration of the treatment. On the other hand, a large Latin American trial [18] found a 5.6% higher eradication rate with a 14-day triple therapy when compared to a 10-day sequential therapy. That was a multicenter study of seven sites and sequential therapy was not significantly better in any of the sites.

Four recent systematic reviews and meta-analyses [7-9, 19] examined the results of sequential treatment regimens against standard triple therapies. Findings of those studies were mostly in favor of sequential treatment; however, eradication rates were suboptimal, indicating the need for more effective treatments.

Several hypotheses have been put forward to explain the observed superiority of sequential treatment. A proposed mechanism involves the effect of amoxicillin on the bacterial wall during the initial 5-day period that prevents the development of resistance against clarithromycin, rendering the bacteria more susceptible to clarithromycin. This also helps prevent the occurrence of cross-resistance. The second 5-day period is associated with an effect of clarithromycin on the bacterial nucleic acid, limiting protein synthesis, regulating acidity, and enhancing the synergy between different antimicrobials. The overall effect is an increased rate of H. pylori eradication.

In the present study, the two treatments resulted in similar rates of eradication, and both treatments were relatively ineffective (success rates 63.6% and 64.1% for the standard and alternative strategies, respectively). Treatments were generally well tolerated by the patients, only 6 requiring treatment discontinuation due to side-effects. We believe that vomiting and nausea observed in patients receiving the alternative regimen are most likely due to the effect of metronidazole.

Although a sequential treatment appears to represent a plausible alternative to standard H. pylori eradication regimen involving triple therapy, more prolonged courses of treatment may be required in certain populations to achieve higher success rates. A sequential treatment scheme consisting of 7 days of two-drug plus 7 days of triple drug; 10 days of two-drug plus 10 days of triple drug; or 14 days of two-drug plus 7 days of triple drug regimen may probably lead to higher success rates. Also, use of other antimicrobial agents may help decrease the rates of metronidazole-associated side effects and metronidazole resistance. Further studies comparing alternative sequential eradication schemes are warranted to better elucidate the role of this approach in H. pylori eradication.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Can Dolapcioglu, Department of Gastroenterology, Dr. Lutfi Kirdar Kartal Research and Training Hospital, Saray Mah. Dorakent Sok., No: 1/C-17 Umraniye, Istanbul 34768, Turkey. Tel: +90 532 2613919; Fax: +90 216 3520083; E-mail: candolapci@hotmail.com

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