Original Article

The Efficacy of Sequential Therapy in Eradication of *Helicobacter pylori* in Turkey

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Abstract

Background and Aim: Most of the studies about sequential therapy that have been reported from Turkey were levofloxacin based. We aimed to compare the *Helicobacter pylori* (*H. pylori*) eradication rates of standard triple, sequential and quadruple therapies including claritromycin regimes in this study. **Materials and Methods:** A total of 160 patients with dyspeptic symptoms were enrolled to the study. The patients were randomized to four groups of treatment protocols. And 40 patients received standard triple therapy for 2 weeks, 40 patients received bismuth containing quadruple therapy for 2 weeks, 40 patients received 5 + 5 clarithromycin-based sequential therapy, and 40 patients received 7 + 7 clarithromycin-based sequential therapy. *H. pylori* eradication was assessed by C 14 urea breath test 4 weeks after therapy. **Results:** Out of 160 patients with *H. pylori* infection, 131 (81.9%) were eradicated successfully and 29 (18.1%) failed to eradicate *H. pylori* infection. *H. pylori* eradication was achieved in 28 of 40 patients receiving standard triple therapy (70%), in 33 of 40 patients receiving quadruple therapy (82.5%), in 37 of 40 patients receiving 5 + 5 sequential therapy (92.5%), and in 33 of 40 patients receiving 7 + 7 sequential therapy (82. 5%). Statistics revealed that 5 + 5 sequential therapy led to significantly higher *H. pylori* eradication rates compared with that of standard triple therapy (P = 0.019). There was no statically difference between 5 + 5 sequential therapy and the other therapy groups' eradication rates, but it was higher than all of the protocols. *H. pylori* eradication rate with sequential therapy in our patients with nonulcer dyspepsia was higher than those of patients with standard therapy (93% versus 82%, respectively, P>0.05). **Conclusion:** 5 + 5 sequential therapy was associated with significantly higher eradication rate of *H. pylori* compared with standard triple therapy in our study cohort.

Keywords: *H.pylori, sequential therapy, eradication protocols*

Date of Acceptance:
05-Jul-2016

Introduction

Helicobacter pylori (*H. pylori)* plays a crucial role in the pathogenesis of chronic gastritis, peptic ulcer disease, gastric-mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma. The treatment of duodenal ulcer mainly depends on *H. pylori* eradication and proton pump inhibitor (PPI). According to the European, American, and Asia- Pacific guidelines, the indications for *H. pylori* eradication is steadily increasing, including gastric cancer prevention in communities with high prevalance rate of gastric cancer and nonulcer dyspepsia.[1] Therefore, *H. pylori* treatment still remains a challenge for physicians and any first-line therapies should be able to cure the infection in all treated patients.[2] The different studies have found that the success rate following standard regimens is disappointingly low, with values less than 45-60% in some countries.[3-5] This phenomenon most likely depends on an increased bacterial resistance to

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Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/1119-3077.196991

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How to cite this article: Harmandar F, İlikhan SU, Üstündağ Y, Harmandar O. The efficacy of sequential therapy in eradication of *Helicobacter pylori* in Turkey. Niger J Clin Pract 2017;20:616-21.

antibiotics, particularly against clarithromycin the key antibiotic in *H. pylori* treatment.[6] Other reasons of this failure are low compliance to treatment, short period of therapy, side effects of the drugs, bacterial load, smoking, and underlying diseases.[7]

In 2000, Vaira *et al*.[8] conceived a novel therapeutic approach to cure *H. pylori* infection, namely a 10-day sequential therapy, which achieved a very high eradication rate. The sequential therapy is a simple dual therapy including a PPI plus amoxicillin 1 g (both twice daily) given for the first 5 days followed by a triple therapy including a PPI, clarithromycin 500 mg, and tinidazole (all twice daily) for the remaining 5 days. It has been found that *H. pylori* bacterial density in gastric mucosa is a factor involved in the antibiotic therapy outcome. Some studies have found that a high bacterial load is associated with a low eradication rate.[9,10] A dual therapy (PPI plus amoxicillin) administered for less than 7 days was able to achieve a cure rate of up to 50%, and that the efficacy of a triple therapy (PPI, clarithromycin, and tinidazole) was inversely related to the bacterial load with higher eradication rates being achieved in those with a low bacterial density in the stomach.[10,11] The use of amoxicillin to which resistance is rare in the initial therapeutic phase has further advantages. It is known that bacteria can develop efflux channels for clarithromycin, which rapidly transfer the drug out of the bacterial cell, preventing binding of the antibiotic to the ribosome. Because amoxicillin acts on the bacterial cell wall and damages it, the initial phase of treatment may prevent the development of efflux channels by weakening the cell wall of bacterium.[3,8,11] Recently in a meta-analysis of 11 randomized, controlled trials, it was shown that the sequential treatment regimen achieved significantly higher eradication rates of 90% compared with standard triple therapy.[12] In Italy, the sequential therapy is now recognized as first-line therapy in the updated Italian guidelines on *H. pylori* management.[1]

Most of the studies about the sequential treatment of *H. pylori* in our country were levofloxacin based. A recent study was reported about clarithromycin- based sequential treatment. That study aimed to compare the efficacy of clarithromycin plus metronidazole and tetracycline plus metronidazole including sequential regimens in Turkey. The eradication rate of the arm of clarithromycin-based therapy was 74.3% and tetracyclin-based therapy was 66.5%. Clarithromycin-based arm's eradication rate was higher, but it was not statically significant and the efficacy of two arms was reported to be similar.[13] Nevertheless, we believe that we need more studies to draw certain conclusions on the success of sequential therapy for *H. pylori* infection in our country. Thus, we planned to investigate and compare the success rates of standard triple, clarithromycin-based sequential and quadruple therapies for *H. pylori* infection. The secondary aim was to evaluate the adherence and adverse events of the regimens.

Materials and Methods

This study was designed as a prospective, randomized controlled trial conducted in outpatient clinics of an academic medical center located in the west Black Sea region of Northern Turkey. Study group consisted of adult patients who went upper endoscopy for the symptoms of epigastric pain and dyspepsia. The biopsies were taken from antrum and went to pathology laboratory for histological examination. A total of 160 patients admitted with the symptoms of epigastric pain and/or dyspeptic symptoms with biopsy proven *H. pylori* infection were enrolled and they were randomized to four groups of treatment protocols. Each group included 40 patients. The standard arm was pantoprazole 40 mg b.i.d., amoxicillin 1 g b.i.d., and clarithromycin 500 mg b.i.d. for 2 weeks. The quadruple therapy consisted of pantoprazole 40 mg b.i.d., metronidazole 500 mg b.i.d., tetracycline 500 mg 4 × 1, and bismuth salt 4 × 300 mg for 2 weeks. The first sequential treatment arm was pantoprazole 40 mg b.i.d. and amoxicillin 1 g b.i.d. for 5 days followed by pantoprazole 40 mg b.i.d., clarithromycin 500 mg b.i.d., and metronidazole 500 mg b.i.d. for the next 5 days. The second arm of sequential treatment regimen had consisted of the same drugs as the first arm of sequential protocol, but these drugs were given on 7 and 7 days basis. *H. pylori* eradication was not assessed by control endoscopic gastric biopsies and we showed *H. pylori* with C-14 urea breath test at least 4 weeks after the completion of treatment protocols.

Statistical analysis

SPSS 19.0 package program was used for statistical analysis. Continuous variables were given with mean, standard deviation, minimum and maximum values. Shapiro-Wilk test was used for test of normality. Pearson Chi-square test was used for group comparisons of categorical variables. Kruskal- Wallis test was used to compare continuous variables between four groups. All comparisons with *P* values lower than 0.05 were assumed as statistically significant.

Results

A total of 160 patients were enrolled to the study and randomized to four-study arms of treatment regimen. All of them completed their regimens. The patients in both treatment arms had comparable demography [Table 1].

When we looked at the efficacy of the endoscopic findings on *H. pylori* eradication rates, we saw that the

endoscopic findings did not affect the result of treatment rates ($P = 0.90$). A total of 17 patients had gastric ulcer and 14 of them were eradicated of *H. pylori* infection. And 30 patients had bulber ulcer and 24 of them were eradicated and 91 of 111 patients with gastritis were eradicated. We also noticed that there was not any correlation between histological findings and eradication rates either ($P = 0.6$) [Table 2].

The most frequent side effects that were reported by patients are drug taste and increasing dyspeptic symptoms with clarithromycin. Some of the patients had been complaining about the metallic taste of metronidazole and glossitis was reported from two of them. Two of the patients could not complete their regimens and these patients were both taken the treatment protocol of the quadruple therapy which consisted of pantoprazole 40 mg b.i.d., metronidazole 500 mg b.i.d., tetracycline 500 mg 4 × 1, and bismuth salt 4 × 300 mg for 2 weeks. They could not complete because of the side effects of the drugs. One of them filed a complaint about metallic taste of drug and the other one allowed the drug because he had glossitis. If we compared the adverse effects of each protocol, we saw that there was no significant difference between each other. After completing the eradication regimens, all treatment groups had taken PPI for 4 weeks and then 2 weeks after *H. pylori* eradication was assessed by C14 urea breath test. When we looked at all of 160 patients, 131 (81.9%) of them were eradicated and 29 (18.1%) of the patients could not be eradicated. *H. pylori* eradication was achieved in 28 of 40 patients (70%) receiving standard triple therapy, in 33 of 40 patients (82.5%) receiving quadruple therapy, in 37 of 40 patients (92.5%) receiving 5 + 5 sequential therapy, and in 33 of 40 patients (82.5%) receiving 7 + 7 sequential therapy [Figure 1].

Although the differences between side effects of the treatment regimens were similar, the sequential therapy regimes were better tolerated with lesser side effects compared with other two regimens. Statistics also revealed that 5 + 5 sequential therapy led to significantly higher *H. pylori* eradication rates compared with that of standard triple therapy ($P = 0.019$). There was no difference between 5 + 5 sequential therapy and the other therapy groups with regard to *H. pylori* eradication rates. This rate of *H. pylori* eradication was found to be higher with 5 + 5 sequential therapy than that of triple therapy in patients with nonulcer dyspepsia, but the difference was not significant statistically (93% versus 82%, respectively, $P = 0.45$).

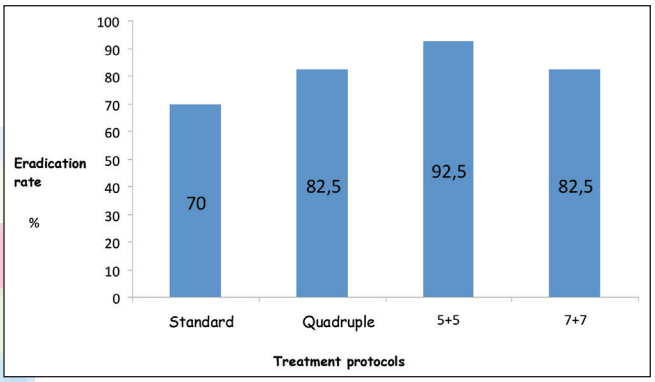

Figure 1: Success of *Helicobacter pylori* eradication with regard to the treatment protocols in our study are seen

Table 1: Baseline demographic data of groups

Demographic parameters	Standard triple group	Quadruple group	5 + 5 Sequential group	7+7 Sequential group	*P*
Age (year)	54.1 ± 13.1	48.5 ± 12.1	46.5 ± 11.6	45.5 ± 14.2	*P*>0.05
Sex (Male/female)	[9[1]] /21	18/22	23/17	17/23	*P*>0.05

Table 2: The histological and endoscopic findings of the patients

Parameters	Standard triple (*N* = 40)	Quadruple treatment (*N* = 40)	5+5 sequential (*N* = 40)	7+7 sequential (*N* = 40)
Endoscopic findings				
Gastric ulcer	6	6	4	1
Duodenal ulcer	8	7	10	6
Erythematous gastropaty	25	26	26	33
Gastric adenocarcinoma	1	1	-	-
Histological findings	24	32	26	28
Chronic gastritis	12	6	12	10
İntestinal metaplasia	3	-	2	1
Atrophy	-	1	-	1
Atrophy + metaplasia	1	1	-	-
Adenocarcinoma				

Discussion

H. pylori infection is a worldwide disease causing significant morbidity and mortality. Current international guidelines advise its eradication for several clinical conditions, including patients with nonulcer dyspepsia, peptic ulcer, gastric mucosa-associated lymphoid tissue -lymphoma, those with gastric remnant for gastric cancer and first-degree relatives of these patients, and in those patients with idiopathic thrombocytopenia. The ideal treatment a single drug able to cure all infected patients is not currently available. The efficacy of currently advised 7-14 days triple therapy is decreasing worldwide with disappointing low eradication rate in several countries.[8] Different studies have found that the success rate following such regimens is disappointingly low, with values less than 45-60%.[8] The ideal antimicrobial therapy should have an eradication rate of at least 90%, a low incidence of significant side effects and should be available worldwide. The main reason of treatment failure is increasing clarithromycin and imidazole resistance. Thus, the standard triple therapy was suggested in the countries that have lower resistance rate less than 15-20% for clarithromycin and 40% of metronidazole.[14] All these observations clearly suggest that more efficacious therapy regimens are required as an initial therapy for clinical practice, the best first-line treatment being still regarded as the best rescue therapy. In 2000, Vaira *et al*.[8] conceived a novel therapeutic approach to cure *H. pylori* infection, namely a 10-day sequential therapy, which achieved a very high eradication rate. Sequential therapy seems to be the most effective first-line therapy available at the moment, being distinctly superior to standard triple therapy as pointed out on more than 2,300 treated patients and the cumulative eradication rate was more than 90%. Some trials showed that cytotoxic strains were more successfully treated than noncytotoxic bacteria and confirmed that peptic ulcer disease was more easily treated than nonulcer dyspepsia.[15] Recent experience from Italy corroborated the hypothesis that the CagA gene is a real predictor of *H. pylori* eradication. If the infection is made by Cag A (+) *H. pylori* bacteria, that shows that it is cytotoxic, it can be eradicated more easily. It was also suggested that sequential therapy was equally effective in CagA (+) and CagA (−) bacteria.[15]

The reports from our country on *H. pylori* eradication regimes were almost designed with tetracyclin or levofloxacin and only one study from south-east part of Turkey reported about clarithromycin-based sequential therapy.[13] When we looked at this study's treatment protocol, the first group was given lansoprazole 30 mg b.i.d. plus amoxicillin 1 g b.i.d. for the 1st week, followed by lansoprazole 30 mg b.i.d., clarithromycin 500 mg b.i.d., and metronidazole 500 mg t.i.d. for the 2nd week. The second arm was given the same regimen including tetracycline 500 g q.i.d. instead of metronidazole. In the study, *H. pylori* eradication rates of sequential therapy based on clarithromycin with metronidazole or tetracycline were low and similar as 74% and 66.5%. We believe that the contrasting difference in this study's results and ours with regard to *H. pylori* eradication rates of clarithromycin-based sequential therapies may be due to regional differences in the clarithromycin resistance rates in our country. Moreover, it was reported from Italy that clarithromycin can also be effective in *H. pylori*'s eradication even in the presence of resistance.[16] The last study about *H. pylori* and sequential treatment that was reported from our country was based on comparing quadruple treatment and different sequential quadruple treatment. In that study, the first arm of study group received standard 14-day quadruple treatment (rabeprazole 20 mg b.i.d., bismuth subcitrate (120 mg q.i.d.), tetracycline 500 mg q.i.d., metronidazole 500 mg t.i.d.) for 2 weeks and the second arm received the modified sequential therapy as 20 mg rabeprazole and 1g amoxicillin, twice daily for the first 5 days, followed by rabeprazole 20 mg b.i.d., bismuth subcitrate (120 mg q.i.d.), tetracycline 500 mg q.i.d., metronidazole 500 mg t.i.d. for the remaining 5 days (10-day sequential therapy group), for the remaining 7 days (12-day sequential therapy group) and for the remaining 9 days (14-day sequential therapy group). The results were not statistically different between the groups regarding *H. pylori* eradication rates (76.5%, 71.4%, 82.4%, and 83.3%, respectively).[17]

In our country, some of the studies about sequential therapy including levofloxacin or tetracyclin showed similar eradication rates compared with standard triple therapy.[18,19] Maastricht III reports suggest an alternative treatment regimen in the geographical areas that have claritromycin resistance more than 20%. In our country, *H. pylori*'s resistance to clarithromycin was reported to be more than 15% [13,17] and that's why the studies about sequential therapy were usually including levofloxacin and or metronidazole. However, the results were noted to be different in these studies with various eradication rates some of them were high and some of them were low. The eradication rates of a pilot study evaluating sequential administration of a PPI-amoxicillin followed by a PPI-metronidazole-tetracycline in Turkey was 57% and another study that was based on levofloxacine revealed 71% rate of *H. pylori*.[18,19] In our study, clarithromycin-based sequential therapy regimen was used and the eradication rates were found to be 92.5% which was significantly higher than that of standard

triple therapy. Although we cannot omit the possibility of regional differences in the rate of clarithromycin resistance in our country, our results supported that, clarithromycin-based sequential therapy has high efficacy even in the areas where there is potentially high clarithromycin resistance.

Although the reason was unknown, the trials showed that standard triple therapy has lower eradication rates on the patients with nonulcer dyspepsia than ulcer dyspepsia. The presence of the CagA gene is a strong predictor of successful treatment. This factor becomes irrelevant when sequential therapy is used according to some studies. Some trials showed that sequential therapy's eradication rates on *H. pylori* in patients with nonulcer dyspepsia were higher than that of standard triple therapy (97% versus 73%, respectively).[15] According to the results of nine trials which compared sequential therapy and 7-day triple therapy in a total 2,299 patients, the overall eradication rates were 97.7% in sequential therapy and 81.2% in 7-day triple therapy for patients with peptic ulcer. For patients with nonulcer dyspepsia, the pooled cure rates were 91.6% with sequential therapy and 72.9% with standard triple therapy.[20] When we looked at our study's results, the eradication rates of sequential therapy for the patients with nonulcer dyspepsia were higher than triple therapy, too. In our study, in standard triple therapy group, *H. pylori* was eradicated in 18 of 27 patients with eradication rates of 82% and in sequential group 24 of 26 were successfully eradicated with eradication rates of 93%. European guidelines suggested 14-day triple therapy instead of 7-day or 10-14 day quadruple therapy for increasing the efficacy of *H. pylori* treatment at the areas that have 15-20% clarithromycin resistance. Some trials showed that the results were similar with 14-day and 7- day triple therapy. Although we used 14-day triple therapy regimen, our eradication rates were as low as 70%. When we looked at the trials with quadruple therapy, some of them achieved high eradication rates with 90-100% and some of them low eradication rates with 60-84%.[21] A treatment protocol that have included using a lot of drugs decreases the patients' compliance for this protocol. The high number of drugs to treat *H. pylori* decreases the compliance and the toxicity of bismuth has been worried in quadruple therapy. Three trials about quadruple therapy showed that the eradication rates were not different between triple and quadruple therapies.[22-24] Some authors reported that 7-day quadruple therapy was enough even in the presence of metronidazole resistance, the others indicated that the quadruple therapy was not enough for *H. pylori* eradication if there is metronidazole resistance.[25-27] In our study, quadruple therapy's eradication rate was found to be higher than that of triple therapy (82.5-70%, respectively). However, the difference was not statically significant and it was lower than sequential therapy (82.5-92.5%, respectively).

Ideal eradication therapy must have high efficacy, good compliance, low toxicity, and low cost. As the European guidelines suggested first-line therapy, 7- day triple therapy has good compliance, low adverse effects, and low cost. Unfortunately, the efficacy of this triple therapy is progressively decreasing worldwide. The eradication rates of triple therapy were noted to be less than 80% according to the many studies. The results of the trials about 5 + 5 sequential therapy reveal that the eradication rates were more than 90% for the patients with ulcer type dyspepsia and nonulcer dyspepsia.[20,28]

Conclusion

The sequential therapy with 5 + 5 days protocol was associated with a significantly higher eradication rate of *H. pylori* compared with standard triple therapy in our study. There seems to be differences in the success of clarithromycin-containing sequential therapies in our country which may be partly related to differences in clarithromycin resistance rates in different parts of our country. In our region, clarithromycin-based sequential therapy seems to be a better strategy than the standard triple therapy and we believe that it should be used as a first-line option for *H. pylori* eradication treatment for our patients. However, we need further studies from the other parts of our country to support or oppose our findings to make certain conclusions on the best eradication regimen for *H. pylori*-infected patients in Turkey.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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