

## Comparison of the efficacy of six different *Helicobacter pylori* eradication regimens: greater than or equal to another.

Mesut Sezikli<sup>1\*</sup>, Goktug Sirin<sup>2</sup>, Züleyha Akkan Cetinkaya<sup>3</sup>, Alpaslan Tanoglu<sup>4</sup>, Fatih Guzelbulut<sup>5</sup>, Fatih Bunul<sup>6</sup>, Gökhan Dindar<sup>7</sup>

<sup>1</sup>Department of Gastroenterology, Kocaeli Derince Education and Research Hospital, Kocaeli, Turkey

<sup>2</sup>Department of Gastroenterology, Kocaeli University School of Medicine, Kocaeli, Turkey

<sup>3</sup>Department of Gastroenterology, Züleyha Akkan Cetinkaya, Medical Park Gebze Hospital, Kocaeli, Turkey

<sup>4</sup>Department of Gastroenterology, Alpaslan Tanoglu, Haydarpaşa Sultan Abdülhamid Education and Research Hospital, Istanbul, Turkey

<sup>5</sup>Department of Gastroenterology, Fatih Guzelbulut, Haydarpaşa Numune Education and Research Hospital, Istanbul, Turkey

<sup>6</sup>Department of Internal Medicine, Fatih Bunul, Siverek State Hospital, Şanlıurfa, Turkey

<sup>7</sup>Department of Gastroenterology, Gökhan Dindar, Kocaeli Derince Education and Research Hospital, Kocaeli, Turkey

### Abstract

**Objective:** This study aimed to compare *H. pylori* eradication rates of different therapy regimens that are commonly used and investigated.

**Methods:** The study included 210 patients with *H. pylori* positive nonulcer dyspepsia, who were randomised into 6 groups. Group 1: Rabeprazole 20 mg BID+amoxicillin 1000 mg BID for the first 7 d and rabeprazole 20 mg BID+amoxicillin 1000 mg BID+clarithromycin 500 mg BID+metronidazole 500 mg TID for the second 7 d. Group 2: Rabeprazole 20 mg BID+amoxicillin 1000 mg BID for the first 5 d and rabeprazole 20 mg BID+clarithromycin 500 mg BID+metronidazole 500 mg TID for the second 5 d. Group 3: Rabeprazole 20 mg BID+metranidazole 500 mg TID+tetracycline 500 mg QID+bismuth QID for 14 d. Group 4: Rabeprazole 20 mg BID+clarithromycin 500 mg BID+amoxicillin 1000 mg BID for 14 d. Group 5: Rabeprazole 20 mg BID+amoxicillin 1000 mg BID+clarithromycin 500 mg BID +metronidazole 500 mg TID for 7 d. Group 6: Rabeprazole 20 mg BID+amoxicillin 1000 mg BID +clarithromycin 500 mg BID+metronidazole 500 mg TID for 14 d.

**Results:** *H. pylori* eradication rates were 65.6%, 68.6%, 56.7%, 51.4%, 65.6% and 62.9% respectively, included in the ITT analysis, and 68.6%, 68.6%, 62.9%, 51.4%, 68.6% and 62.9% respectively, included in the PP analysis for all groups. There was no significant difference between the groups with regard to eradication rates.

**Conclusion:** Although *H. pylori* eradication rates of hybrid, sequential and concomitant therapy regimens were higher than those of quadruple and standard triple therapy regimens, they were also far from the ideal rate.

**Keywords:** *Helicobacter pylori*, Hybrid therapy, Sequential therapy, Quadruple therapy, Concomitant therapy.

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### Introduction

The prevalence of *Helicobacter pylori* is as high as 90% in developing countries. *H. pylori* infection is associated with chronic gastritis that may progress into Peptic Ulcer Disease (PUD), gastric adenocarcinoma, and mucosa associated lymphoid tissue lymphoma (MALToma) [1,2]. In 1994, *H.*

*pylori* was defined as a grade 1 carcinogen by the World Health Organization.

Although *H. pylori* infection can be diagnosed easily, eradication can be difficult. *H. pylori* eradication rates are low due to resistance to antibiotics, especially in regions where unnecessary antibiotic use is common. Indications for *H. pylori* therapy were defined by the Maastricht IV consensus report. According to the Maastricht IV consensus report, standard

triple therapy, which consists of a Proton Pump Inhibitor (PPI) plus clarithromycin plus amoxicillin/metronidazole for 14 d, is recommended in regions where the clarithromycin resistance rate is lower than 15-20%. With time, *H. pylori* eradication rates with such regimens have decreased [3].

In a randomized controlled study, eradication of *H. pylori* led to a 25% reduction in dyspepsia consultations after 2-7 y of follow-up. Similar results were also reported in Turkey [4,5]. Despite discrepant results, in Turkey the *H. pylori* eradication rate is lower than the ideal 80%. In this study, various therapy regimens (i.e. standard triple therapy, quadruple therapy, concomitant therapy, hybrid therapy, and sequential therapy) were given to similar patient groups. We aimed to compare *H. pylori* eradication rates using these different therapy regimens that are routinely applied in clinical practice.

## Materials and Methods

The study included 210 patients who were admitted to the Kocaeli Derince Education and Research Hospital Gastroenterology Outpatient Clinic with *H. pylori* positive nonulcer dyspepsia in 2015 (January-December). All subjects were informed about the study protocol, and written consent was obtained from all participants. The presence of *H. pylori* was assessed *via* histological examination. Two samples were taken from the gastric antrum and corpus for histological assessment and rapid urease test during upper gastrointestinal endoscopy. Exclusion criteria included a history of previous *H. pylori* eradication therapy, upper gastrointestinal surgery or gastric malignancy, impaired liver or renal function, pyloric stenosis, pregnancy or breastfeeding, and a history of allergy to penicillin or any other antibiotic. To prevent any interference with *H. pylori* eradication, patients who had taken bismuth salts, nonsteroidal antiinflammatory drugs, PPIs, H<sub>2</sub> receptor blockers, antibiotics, or probiotics within the previous 4 w were also excluded.

Six different therapy regimens were prescribed to patients. Therapy regimens are given in Table 1. The regimen given to each patient was chosen by lot, in that a number from 1 to 6 was written on a piece of paper, 35 pieces of each number were enclosed in a bag and one piece was chosen by each patient. Patients underwent a urea breath test (UBT) 4-6 w after completion of therapy. Patients were warned not to take any PPI or antibiotic during this time. Adverse events were

recorded. Patients who took at least 80% of the scheduled doses of the prescribed regimen were accepted as compliant.

All patients were evaluated with Intention-to-Treat (ITT) analysis, in which patients without a final *H. pylori* determination or with protocol violations were considered treatment failures. Per-Protocol (PP) analysis included all subjects that took at least 80% of the scheduled doses of the prescribed regimen and completed the final *H. pylori* status assessment. Statistical calculations were performed using SPSS version 11.0, 2000 software (SPSS Inc., Chicago, IL, USA). Results are presented as mean  $\pm$  standard deviation for quantitative variables, and as number and percentage for qualitative variables. The difference in *H. pylori* eradication rate between the groups was assessed using the  $\chi^2$ -test. Probability values less than 0.05 were considered significant.

## Results

The study included 210 patients. All patients were Caucasian, and 90 of them (42.9%) were men with a mean age of 42.39  $\pm$  12.01 (18-79 y). Demographic characteristics of the groups are shown in Table 2. There was no statistically significant difference between the groups with regard to age and gender.

The patients were randomized to group 1 (hybrid), group 2 (sequential), group 3 (quadruple), group 4 (standard triple), group 5 (concomitant 1) and group 6 (concomitant 2) for *H. pylori* eradication. In total, 11 patients (3 in group 1, 5 in group 3 and 3 in group 5) did not return for the post-treatment follow-up. In all, 210 and 199 patients were enrolled in the ITT and PP analysis, respectively.

*H. pylori* eradication was achieved in 21 of the 35 patients (65.6%) in group 1, 24 of the 35 patients (68.6%) in group 2, 17 of the 35 patients (56.7%) in group 3, 18 of the 35 patients (51.4%) in group 4, 21 of the 35 patients (65.6%) in group 5 and 22 of the 35 patients (62.9%) in group 6 and were included in the ITT analysis. There was no statistically significant difference between the groups with regard to eradication rates (Table 3).

The most frequent adverse events were diarrhea, nausea, metallic taste, constipation and dizziness. Adverse events were more frequent in group 4 than in the other groups (14/35, 40%) (p: 0.04) (Table 4). However, adverse events were mild and did not lead to early discontinuation of therapy in any patient.

**Table 1.** *Helicobacter pylori* therapy regimens.

Group 1	Rabeprazole 20 mg BID plus amoxicillin 1000 mg BID for the first 7 d, rabeprazole 20 mg BID plus amoxicillin 1000 mg BID plus clarithromycin 500 mg BID plus metronidazole 500 mg TID for the second 7 d
Hybrid	
Group 2	Rabeprazole 20 mg BID plus amoxicillin 1000 mg BID for the first 5 d, and rabeprazole 20 mg BID plus clarithromycin 500 mg BID plus metronidazole 500 mg TID for the second 5 d
Sequential	
Group 3	Rabeprazole 20 mg BID plus metronidazole 500 mg TID plus tetracycline 500 mg QID plus bismuth QID for 14 d

Quadruple	
Group 4	Rabeprazole 20 mg BID plusclarithromycin 500 mg BID plusamoxicillin 1000 mg BID for 14 d
Standard triple	
Group 5	Rabeprazole 20 mg BID plusamoxicillin 1000 mg BID plusclarithromycin 500 mg BID plusmetronidazole 500 mg TID for 7 d
Concomitant 1	
Group 6	Rabeprazole 20 mg BID plusamoxicillin 1000 mg BID plusclarithromycin 500 mg BID plusmetronidazole 500 mg TID for 14 d
Concomitant 2	

**Table 2.** Demographic characteristics of the patients.

	Male, n (%)	Female, n (%)	Age (y) (mean ± SD)
Group 1	9 (25.7%)	26 (74.3%)	43.82 ± 14.7
Group 2	19 (54.3%)	16 (45.7%)	44.28 ± 13.4
Group 3	17 (48.6%)	18 (51.4%)	40.54 ± 9.47
Group 4	16 (45.7%)	19 (54.3%)	38.80 ± 12.26
Group 5	16 (45.7%)	19 (54.3%)	43.91 ± 12.80
Group 6	13 (37.1%)	22 (62.9%)	43.00 ± 14.67
Total	90 (42.9%)	120 (57.1%)	42.39 ± 13.6

**Table 3.** Eradication rates of the groups.

	Eradication rate no.	Eradication rate %	ITT/PP, p value
Group 1-hybrid	21	65.6/68.6	>0.05
Group 2-sequential	24	68.6/68.6	>0.05
Group 3-quadruple	17	56.7/62.9	>0.05
Group 4-standard triple	18	51.4/51.4	>0.05
Group 5- concomitant 1	21	65.6/68.6	>0.05
Group 6- concomitant 2	22	62.9/62.9	>0.05

**Table 4.** Rates of adverse effects in the therapy groups.

	Rate (%)	p-value
Group 1-hybrid	12.5	
Group 2-sequential	22.9	
Group 3-quadruple	14.8	
Group 4-standard triple	40	0.04
Group 5-concomitant 1	18.2	
Group 6-concomitant 2	19.4	

Total	22.1
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## Discussion

Although the association between *H. pylori* and PUD, gastric adenocarcinoma, and MALToma is well established, eradication of *H. pylori* remains difficult. To be accepted as successful, any given therapy regimen should provide at least an 80% eradication rate [6]. However, it is usually impossible to achieve this goal. The same drugs are used in various combinations and doses for different durations to increase eradication rates. Eradication rates are low especially in regions where resistance to clarithromycin and metronidazole is common. In fact, regional differences in eradication rates have been shown in recent studies.

The *H. pylori* eradication rate of standard triple therapy has been shown to be low in Turkey. The eradication rate of this regimen was 63.6% in the study of Avşar et al, 57% in the study of Polat et al. and 82.4% in the study of Rakici et al. [7-9]. In the study of Rakici et al., eradication of *H. pylori* was assessed by stool antigen testing, which may lead to false negative results due to standardization issues [10]. The eradication rate of this regimen has been shown to be lower than the ideal rate in European studies as well [3].

Although a standard triple therapy regimen is not recommended in high clarithromycin resistance regions, it is commonly given due to its ease of use in clinical practice. In the present study, adverse events of this regimen were more frequent than those of other regimens; however, they were not so severe as to lead to early discontinuation of therapy.

The *H. pylori* eradication rate of bismuth containing quadruple therapy was 56.7% in the present study, which is much lower than the ideal rate. According to the Maastricht IV consensus report, bismuth containing quadruple therapy is recommended as a first-line therapy, especially in areas with a high prevalence (>20%) of clarithromycin resistance [3]. In a 2012 study by Kadayifci et al., the *H. pylori* eradication rate of bismuth containing quadruple therapy regimen was 79% [11]. In another study, the eradication rate with the same regimen was 47.1%, demonstrating that eradication rates with the same regimen can be different in the same region [12]. In the present study, the eradication rate was quite a bit lower than the ideal rate. Early treatment discontinuation was also higher in this

group as compared to others, which might be due to adverse events of the drugs in this regimen.

Hybrid therapy combines the sequential and concomitant therapy regimens with 7 d of dual therapy (PPI and amoxicillin) followed by 7 d of quadruple therapy (a PPI, amoxicillin, clarithromycin and metronidazole) [13]. Some studies have reported this therapy to achieve high eradication rates [13,14].

The eradication rate of hybrid therapy was 65.6% in the present study, which was also lower than the ideal rate. In Turkey, there has been no study to date evaluating the efficacy of hybrid therapy. In an Iran study, the eradication rates of 10- and 14 d hybrid therapy regimens were 77.6% and 86.7%, respectively [15]. There is a need for studies evaluating the efficacy of hybrid therapy consisting of different antibiotics in larger patient groups.

Sequential therapy, which consists of the administration of a PPI and amoxicillin for the first 5 d followed by a PPI, clarithromycin and tinidazole/metronidazole for the remaining 5 d, was pioneered in Italy in 2000 [16]. The superiority of this therapy over standard triple therapy has been widely documented [17].

The *H. pylori* eradication rate of sequential therapy was 68.6% in the present study, which was the highest rate among other regimens. In a study by Erdur et al. from Turkey, the *H. pylori* eradication rates of standard therapy and sequential therapy were 46.4% and 93.7%, respectively [18]. However, this study included children. Moreover, PPI was given for 30 d in combination with antibiotics for 7 d plus 7 d in the sequential therapy arm, which might have resulted in a high eradication rate in that study. These might be the reasons for the high eradication rate of sequential therapy. Even so, it is worthwhile to point out that the eradication rate of the standard therapy regimen was 46.4%.

In another study, Sapmaz et al. compared the efficacy of bismuth-containing quadruple therapy and modified sequential therapy regimens [19]. In sequential therapy arms, patients were given a PPI plus amoxicillin for the first 5 d; however, bismuth subcitrate, tetracycline and metronidazole were given for 5, 7 and 9 d in the second phase. Eradication rates of 10-, 12- and 14 d sequential therapy regimens were 72.5%, 82.5% and 80.0%, respectively; whereas the eradication rate was 77.5% with the standard therapy regimen [19].

Concomitant therapy was first introduced in 1998 but recently reconsidered as a first line therapy [20-22]. Concomitant therapy consists of quadruple therapy with standard triple therapy (PPI, clarithromycin, amoxicillin) plus metronidazole or tinidazole. The duration of treatment is not standardized, and various durations, ranging from 3 to 14 d, have been proposed. However, various studies have demonstrated the high (>90%) efficacy of concomitant therapy, even when administered for only 5 d [23].

Studies evaluating the efficacy of concomitant therapy are also limited in Turkey. In a 2011 study by Toros et al., the

eradication rate of 14 d concomitant therapy was 75% [24]. Kadayifci et al. compared bismuth-containing quadruple therapy and 14 d concomitant therapy, which consisted of tetracycline instead of clarithromycin. The *H. pylori* eradication rate was 79% in the bismuth-containing quadruple therapy group and 75% in the concomitant therapy group [11]. In the present study, eradication rates of 7- and 14 d concomitant therapy regimens were similar, being far from the ideal rate.

In the study by Zullo et al, the eradication rates were 85.5% with the concomitant regimen, 91.1% with the sequential therapy, and 80% with the hybrid regimen. Differences were not statistically significant [25].

In a 2013 review, Gatta et al. evaluated 46 randomized trials. In that study, sequential therapy was superior to 7- and 10 d Standard triple therapy, but not superior to 14 d Standard triple therapy, bismuth based therapy, and non-bismuth based therapy [26]. In the present study, sequential therapy was superior to 14 d Standard triple therapy and bismuth-containing quadruple therapy; however, the difference was not statistically significant. Adverse events were also similar and did not result in patient in compliance.

## Conclusions

The superiority of our study was that it was a comparison of six different regimens. Relatively small study population was a limitation of our research. However, prospective nature of our study and strict inclusion and exclusion criterion provides favorability for our research. Moreover in the literature, many studies performed stool Hp antigen tests for testing eradication success although not being validated. But in our research we performed a validated UBT for evaluating Hp eradication rate, which strengthens our results. In Turkey, because of high prevalence of primary antibiotic resistance (clarithromycin 24.8%, metronidazole 33.7%) [27] and reported low Hp eradication rates (40-50%), Standard triple therapy should not be used in Turkey. Although other regimens are superior to Standard triple therapy, their eradication rates were also far from the ideal rate. There is a need for studies based on antibiotic resistance in larger patient groups.

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**\*Correspondence to**

Mesut Sezikli

Department of Gastroenterology

Kocaeli Derince Education and Research Hospital

Turkey