

Comparison of the efficacy and safety of hybrid and sequential therapies as a first-line regimen for *Helicobacter pylori* infection in Turkey

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Abstract

Introduction: *Helicobacter pylori* infection is a common infection worldwide. The most frequently recommended treatment for eradication of *H. pylori* remains triple therapy. In this study, we compared sequential and hybrid regimens for *H. pylori* eradication in a region of Turkey with high resistance to clarithromycin.

Material and methods: Three hundred and forty *H. pylori*-positive patients were enrolled in the study. The subjects were randomly divided into two groups. The first group (170 patients) received rabeprazole (40 mg/b.i.d.) and amoxicillin (1000 mg/b.i.d.) for 2 weeks and metronidazole and clarithromycin (500 mg/b.i.d.) during the second week in the hybrid therapy group. The second group (170 patients) received rabeprazole (40 mg/b.i.d.) for 14 days, amoxicillin (1000 mg/b.i.d.) for the first 7 days, and metronidazole plus clarithromycin (each 500 mg/b.i.d.) during the next 7 days in the sequential therapy group.

Results: In the per-protocol analysis, the eradication rate in the hybrid therapy group was 96.1% (147/153), and in the sequential therapy group it was 90.9% (140/154). There was no significant difference between the two groups ($p = 0.06$). Ninety-seven of those 340 patients reported minor adverse drug reactions. The percentages of patients with adverse reactions were 30.6% in the hybrid therapy group and 26.5% in the sequential therapy group ($p = 0.74$).

Conclusions: Both therapies are highly effective for eradication of *H. pylori*, and could be recommended as a first-line therapy in regions with high antibiotic resistance.

Key words: *Helicobacter pylori*, hybrid regimen, sequential regimen.

Introduction

Helicobacter pylori infection is a common infection worldwide and is well recognized to be the main cause of gastritis, peptic ulcers, and gastric cancer [1]. Triple therapy, which contains a proton pump inhibitor (PPI) and amoxicillin with either clarithromycin or metronidazole, is a standard first-line eradication regimen [2, 3]. However, in most countries, the eradication success of triple therapy has been reported to have decreased below acceptable levels ($\leq 80\%$) because of the increasing

rate of *H. pylori* resistance to antibiotics [4, 5]. Therefore, several regimens have been proposed as alternative first-line treatments for *H. pylori* infection, including sequential therapy (ST) and hybrid therapy (HT).

Sequential therapy consists of a PPI (b.i.d) and amoxicillin 1 g (b.i.d) given for 7 days, followed by the PPI (b.i.d), clarithromycin 500 mg (b.i.d), and metronidazole 500 mg (b.i.d) for 7 days. Hybrid therapy is similar with the exception that the amoxicillin 1 g (b.i.d) is continued throughout the 14 days. According to recent studies, these therapies are highly effective and safe, but there are not enough data about the efficacy of these treatments in countries with high clarithromycin and metronidazole resistance rates [6–17].

However, ST and HT regimens both have been reported to be effective. They have little difference in treatment modality. It has been a subject of research whether there is a difference in the eradication rates between the two regimens. In the literature, there have been limited data comparing the differences in the efficacy and safety between these protocols, and conflicting results have been reported.

In this study, we aimed to assess and compare the efficacy and safety of ST and HT protocols in *H. pylori* eradication in Turkey in a region that has high clarithromycin and metronidazole resistance rates.

Material and methods

Subjects

This prospective, single-center study was performed at the Gastroenterology Department of Siirt State Hospital in Turkey, from October 2014 to April 2015. Patients who had biopsy-proven *H. pylori* gastritis were eligible for the study. Exclusion criteria included previous attempts at *H. pylori* eradication therapy, recent use of antibiotic or bismuth salts or proton-pump inhibitors in the last 2 months before the study, chronic use of nonsteroidal anti-inflammatory drugs or corticosteroids, severe comorbid diseases, gastric malignancy including adenocarcinoma and lymphoma, pregnancy or lactation, diarrhea, prior gastric surgery, allergy to any of the drugs in the current treatment, and age under 18 years. Informed consent was obtained from each patient before enrolling them in the study.

The patients were randomly given ST and HT protocols. Patients in the ST group were given rabeprazole 40 mg (b.i.d, 30 min before meals) and amoxicillin 1000 mg (b.i.d, 1 h after meals) for the first 7 days of the treatment period and then rabeprazole 40 mg (b.i.d, 30 min before meals), clarithromycin 500 mg (b.i.d, 1 h after meals), and metronidazole 500 mg (b.i.d, 1 h after meals). During the remaining 7 days, patients in the HT

group were given the same treatment with the exception that amoxicillin 1 g (b.i.d) was continued up to the 14th day.

A detailed written treatment protocol was given to all patients to prevent misuse of medications. They were actively interviewed about side effects and treatment adherence using a structured questionnaire 1 week after the end of the treatment. To confirm patient compliance, we asked the patients to bring their remaining medication and counted the rest of their pills. Patients with a compliance rate of less than 80% were excluded from the study per-protocol (PP) analysis. Eradication rates of *H. pylori* were measured by the ¹³C-urea breath test (¹³C-UBT). Six weeks after the treatment period, and after at least 2 weeks with no administration of PPI, we confirmed *H. pylori* eradication using ¹³C-UBT.

Statistical analysis

Both PP (excluding patients with poor compliance of therapy and patients with unavailable data after therapy) and intention to treat (ITT) (including all eligible patients enrolled in the study regardless of compliance with the study protocol; patients with unavailable data are assumed to have been unsuccessfully treated) analyses were used to evaluate the *H. pylori* eradication rate. Data analysis was performed using the statistical software package program IBM SPSS for Windows (version 19.1; SPSS Inc., Chicago, IL, USA). Inter-group comparisons of categorical variables were done using the χ^2 test, and continuous variables were compared using Student's *t*-test. Categorical variables were presented as percentages or counts, and continuous variables were presented as means and standard deviations in the descriptive analysis. By setting the significance level to $p < 0.05$, the statistical power to 90%, and the drop-out rate to 10%, we calculated a need for 170 patients in each group.

Results

Patient characteristics

There was no significant difference between the average ages of the groups, which were 37.2 ± 13.2 in the ST group and 38.1 ± 12.1 in the HT group ($p = 0.50$). The gender distribution was also similar between groups ($p = 0.51$). There was no significant difference in relation to endoscopic findings between the groups ($p = 0.69$) (Table I).

Eradication rate for first-line treatment

In the ITT analysis, the eradication rates were 82.4% (140/170) for the ST group and 86.5% (147/170) for the HT group. There was no signifi-

Table I. Characteristics of patients

Parameter	HT	ST	P-value
Age [year]	38.08 ±12.0	37.19 ±13.2	0.5
Gender:			0.51
Male	50.6%	54.1%	
Female	49.4%	45.9%	
Diagnosis:			0.69
Gastric ulcer	14.1%	11.2%	
Duodenal ulcer	19.4%	21.2%	
Gastritis	66.5%	67.6%	
Consumption:			
Smoking	19.4%	17.6%	0.67
Alcohol	2.4%	2.9%	0.73

HT – hybrid therapy, ST – sequential therapy.

cant difference between the two groups ($p = 0.29$) (Table II).

The PP analysis was performed on 154 patients in the ST group and 153 patients in the HT group. We excluded patients who did not come for UBT (10 patients in the ST group and 9 patients in HT group) and who had poor adherence to the treatment ($n = 6$ in the ST group and 8 in the HT group). In the PP analysis, the eradication rates were 90.9% (140/154) for the ST group and 96.1% (147/153) for the HT group. There was no significant difference in eradication rates between the two groups ($p = 0.06$) (Table III, Figure 1).

Adverse drug reactions

Ninety-seven of the 340 patients reported minor adverse drug reactions. The percentages of patients with adverse reactions were 26.5% (45/170) in the ST group and 30.6% (52/170) in the HT group ($p = 0.74$). The percentages of patients who discontinued the treatment due to ad-

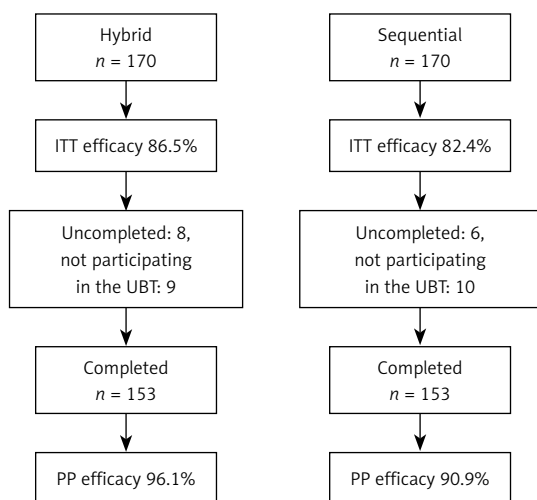


Figure 1. Hybrid and sequential therapies

ITT – intention to treat, PP – per protocol.

Table II. *Helicobacter pylori* eradication rates in the 14-day hybrid and sequential therapies

Variable	HT group, rate % (n)	ST group, rate % (n)	P-value
ITT analysis	86.5% (147/170)	82.4% (140/170)	0.29
PP analysis	96.1% (147/153)	90.9% (140/154)	0.06

HT – hybrid therapy, ST – sequential therapy, ITT – intention to treat, PP – per protocol.

Table III. Adverse events in the hybrid and sequential therapies

Parameter	HT	ST	P-value
Pruritus	16 (9.4%)	12 (7.1%)	0.28
Bitter taste	14 (8.2%)	10 (5.9%)	0.31
Loose stool	12 (7.1%)	15 (8.8%)	0.43
Headache	7 (4.1%)	4 (2.4%)	0.38
Abdominal pain	3 (1.8%)	4 (2.4%)	0.57
Total	53 (30.6%)	45 (26.5%)	0.74

HT – hybrid therapy, ST – sequential therapy.

verse events were 3.5% (6/170) in the ST group and 4.7% (8/170) in the HT group.

In order of frequency there were bitter taste, loose stools, and pruritus as the most common adverse reactions in all study groups. Pruritus was the most common adverse reaction in the HT group, and loose stools was the most common event in the ST group. However, these differences were not statistically significant, and there were no major life-threatening adverse reactions (Table III).

Discussion

In the present study, we assessed and compared the efficacy and safety of the ST and the HT protocols as a first-line treatment of *H. pylori* infection in Turkey, which has high clarithromycin and metronidazole resistance rates. We found satisfactory results, which indicate that the eradication rates were 90.9% and 82.4% for the ST group and 96.1% and 86.5% for the HT group in the PP and ITT analyses, respectively. There was no significant difference in eradication rates between the two groups.

The European *H. pylori* study has suggested that treatment regimens should achieve an eradication rate over 80% on ITT analysis and 85% on PP analysis in order to be acceptable as first-line therapy for *H. pylori* eradication [18]. The efficacy of *H. pylori* eradication regimens was also classified based on per-protocol success as follows: A, excellent (> 95%); B, good (90–95%); C, fair (85–89%); D, bad (81–84%); and E, unacceptable (< 80%) [19]. According to this scale, our results showed excellent efficacy (grade A) for the HT protocol and good efficacy (grade B) for the ST protocol.

Since the efficacy of standard triple therapy decreased to an unacceptable level for successful eradication rates in most countries, new strategies have been developed in the last decade [5]. The main factor leading to the high eradication failure rate is increased antibiotic resistance of the bacteria [20]. The prevalence of antibiotic resistance varies considerably by region and is related to the use of antibiotics. Especially, recent data suggest that clarithromycin resistance is a growing problem affecting the eradication rate of *H. pylori*. However, studies from different countries that have high clarithromycin resistance rates have reported that eradication rates with HT ranged from 76.4% to 97.4% [8, 13]. It has been shown in a meta-analysis that the cure rate of the infection is reduced to 55% in patients with clarithromycin resistance [21].

The rate of resistance to clarithromycin has increased gradually in Turkey. Recently, a study on a Turkish dyspeptic population revealed a clarithromycin resistance rate of 40.2%, using the PCR method [22]. Metronidazole resistance is the other main factor responsible for eradication failure in Turkey; a recent study reported a metronidazole resistance rate of 45.5% [23]. This increased incidence of high-level clarithromycin and metronidazole resistance in *H. pylori* is a serious concern, as it negatively affects eradication regimens.

To overcome increasing resistance and eradication failures, many alternative therapeutic strategies that utilize adjusted drug combination, dosage, duration, and timing of the drug administration have been studied. Among these therapies, ST and HT protocols have emerged as the most promising treatments and have been reported to be effective [6–12]. In these protocols, amoxicillin is administered before other antibiotics. Amoxicillin disrupts the bacterial cell wall of *H. pylori* and enables clarithromycin and metronidazole to infiltrate into the bacteria. Due to the disrupted cell wall, *H. pylori* is unable to form an efflux pump to export clarithromycin, and the effect of the antibiotics can be maintained and is effective, even in cases of clarithromycin-resistant *H. pylori* [24–27].

Eradication rates also appear to have significant regional variation. In Turkey, some previous studies were conducted that compared triple therapy and ST; they showed various PP eradication rates ranging from 57% to 88% in ST, which was more effective than triple therapy [22, 28–30]. In addition, ST has been reported to be more effective than triple therapy by studies from Asian countries [31, 32] and many other countries with high clarithromycin resistance rates by meta-analysis [33].

Both ST and HT protocols contain the same drugs, but amoxicillin is used 7 more days in the HT protocol. Because of this difference, studies have been designed around the differences in the effectiveness of the ST and the HT regimens. How-

ever, they have reported conflicting results. Some of them from Taiwan [13], which also has high antibiotic resistance rates, and from Korea have shown no significant differences between the two protocols. One of the Italian studies [7] also showed no significant differences between them, while the other [9] reported that the eradication rate of the HT group was lower than that of the ST group. A recent study from Iran [8] reported that the eradication rate of the HT group was higher than that of the ST group. In the present study, we found that the eradication rate of the HT group was slightly higher than that of the ST group, but this difference was not statistically significant. Our results concur with those of the majority of the previous results.

An acceptable eradication regimen needs good adherence to the treatment and a low incidence of serious adverse events (less than 5%) [34]. Although both regimens require a complex schedule in which the administered drugs should be changed in the second week, and even though there is a concern that these protocols could cause possible misuse, in our study we observed good compliance in both groups. It may also be thought that these protocols can lead to high incidence of adverse events because they contain multiple drugs. In our study, only 14 (4.1%) patients in all study groups discontinued the therapy because of adverse reactions. However, 28.5% of all patients who experienced minor adverse events completed the treatment. Despite the longer administration duration of amoxicillin in the HT protocol, the compliance rates did not differ significantly between the two groups (4.7% in the HT group and 3.5% in the ST group).

The major limitation of our study was the lack of assessment of primary resistance to different antibiotics for *H. pylori* strains. However, our main purpose was to assess the two novel regimens as first-line therapy in clinical practice, and it is not recommended to assay antibiotic resistance tests in first-line treatment.

In conclusion, the HT and ST protocols provide acceptable eradication rates in a region with high resistance to clarithromycin and metronidazole. Both therapies could be recommended as a first-line therapy with high efficacy and safety, and hybrid therapy, which is a novel therapy, could be an alternative to sequential therapy, but further studies are needed to substantiate these findings.

Conflict of interest

The authors declare no conflict of interest.

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