Comparison between different first-line therapy protocols in eradicating *Helicobacter pylori* in a region with high clarithromycin resistance

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Abstract

Introduction: *Helicobacter pylori* infection is encountered in more than 50% of the world population. A high rate of clarithromycin resistance is observed among *Helicobacter pylori* strains in some regions because clarithromycin is a drug commonly used for the treatment of other infections.

Aim: To identify an efficient eradication protocol for patients infected with *H. pylori* and to suggest an alternative first-line therapy particularly in countries with high clarithromycin resistance.

Material and methods: Patients (18–75 years old) having dyspeptic complaints in a 1-year period and diagnosed with *H. pylori* infection by gastric biopsy were included and randomised to three groups, each receiving different sequential eradication therapy (LAM-B: lansoprazole, amoxicillin, metronidazole, bismuth: LAM-T: lansoprazole, amoxicillin, metronidazole, tetracycline; LAM-BT: lansoprazole, amoxicillin, metronidazole, bismuth, tetracycline). Eradication was evaluated via urea breath test.

Results: This study included 166 patients (mean age: 40 ±12 years; female, 68.7%) with *H. pylori* infection. Among them, 50 (30.1%) were in the LAM-B group, 59 (35.5%) were in the LAM-T group, and 57 (34.3%) were in the LAM-BT group. The non-steroidal anti-inflammatory drug use was the lowest in the LAM-BT group. Eradication rates were over 80% and similar in each group, with the highest rate in the LAM-BT group (93%). Adverse event rate was the highest in the LAM-T group. *Helicobacter pylori* eradication was achieved in 143 (86.1%) patients.

Conclusions: The combination regimens without clarithromycin achieved an eradication rate over 80% in all groups. Knowing and monitoring the regional antibiotic resistance rates is important for successful treatment of *H. pylori* infections.

Introduction

Helicobacter pylori (*H. pylori*) is a microorganism that is estimated to cause infection in more than 50% of the world population despite its varying prevalence among geographical regions, and thereby it is responsible for significant morbidity and mortality [1]. *Helicobacter pylori* is associated with active chronic gastritis, peptic ulcer disease, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma and is reported to enhance the risk of developing ulceration and gastric bleeding in individuals using non-steroidal anti-inflammatory drugs (NSAIDs) [1]. Nearly 5% of the total annual cancer cases worldwide have been attributed to *H. pylori* [2].

Urea breath test and endoscopy with biopsy are the major diagnostic tools used to detect *H. pylori* infection [1]. Various combinations of antibiotics are used as eradication treatment. The most common therapeutic recommendations include 1-week triple therapy with proton pump inhibitor (PPI), amoxicillin, and clarithromycin. There are second-line therapies recommended in case the first-line therapy fails. The presence of pre-treatment antimicrobial resistance, nonadherence to treatment, and smoking have been reported among the factors contributing to treatment failure [1].

It has been emphasised that response to the first-line standard treatment of *H. pylori* infection has decreased in recent years. While the eradication rate was over 90% in the beginning, it has been reduced to below 70% in time [3]; one of the reasons for this is the resistance to antibiotics, particularly to clarithromycin. A high rate of clarithromycin resistance is encountered among *H. pylori* strains in some regions because clarithromycin is a drug commonly used for the treatment of other infections [1, 3]. The reported prevalence of clarithromycin resistance in *H. pylori* ranges from 12.5% to 76.2% in different regions of the world [4–8].

In a study from Turkey, which screened the population via urea breath test, the prevalence of *H. pylori* infection was found to be as high as 82.5% [9]. In the studies, the rates of clarithromycin resistance in Turkey have been reported to be 36.7% [10], 47.5% [11], and 48.2% [12].

Aim

The aim of the present study was to identify an efficient eradication protocol for patients infected with *H. pylori* and to suggest an alternative first-line therapy, particularly in countries with high clarithromycin resistance, such as Turkey. In addition, it was aimed to investigate the factors that may have an effect on eradication.

Material and methods

Patients

Patients aged between 18 and 75 years, who presented with dyspeptic complaints in a 1-year period and in whom *H. pylori* was determined by gastric biopsy, were enrolled in the present study in three centres in Ankara. Patients with gastric or duodenal ulcer, those with chronic liver/kidney disease or history of malignancy, those having previous treatment for *H. pylori* infection, and those with a history of PPI, histamine-2 (H2) receptor antagonist, or antibiotic use within the last four weeks were excluded. The present study was approved by the Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital.

Procedures

Gastric biopsy was taken from the gastric antrum and corpus of the patients during endoscopic examination of the upper gastrointestinal system. The patients were diagnosed with *H. pylori* infection based on histopathological examination, and histopathological grading was performed.

The patients infected with *H. pylori* were randomised to three groups, and each group received different sequential eradication therapy. The treatment schedule of the study groups is presented in Table I. Eradication was evaluated via carbon 14-labeled urea breath test (^{14}C-UBT) performed 6 weeks after the completion of treatment.

Factors (age, gender, body mass index, alcohol consumption, smoking, non-steroidal anti-inflammatory drug use, localisation of *H. pylori*, *H. pylori* load, severity of inflammation, degree of activation, and presence of atrophy and intestinal metaplasia) that might have an effect on eradication were assessed.

Histopathological examination

Helicobacter pylori load, severity of inflammation, and degree of activation were graded by the modified Sydney classification [13] using visual analogue scales as follows: 0, normal; 1+, mild; 2+, moderate; and 3+, marked. Moreover, presences of atrophy and intestinal metaplasia were also recorded.

Statistical analysis

Data analyses were performed using PASW Statistics for Windows version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as mean, standard deviation, median, minimum, and maximum for numerical variables. Normal distribution of variables was ana-

Table I. Treatment schedule of the study groups

Week	Treatment groups		
	LAM-B	LAM-T	LAM-BT
1	Lansoprazole 2 × 30 mg	Lansoprazole 2 × 30 mg	Lansoprazole 2 × 30 mg
	Amoxicillin 2 × 1000 mg	Amoxicillin 2 × 1000 mg	Amoxicillin 2 × 1000 mg
2	Lansoprazole 2 × 30 mg	Lansoprazole 2 × 30 mg	Lansoprazole 2 × 30 mg
	Metronidazole 4 × 500 mg	Metronidazole 4 × 500 mg	Metronidazole 4 × 500 mg
	Bismuth 4 × 500 mg	Tetracycline 4 × 500 mg	Bismuth 4 × 500 mg
			Tetracycline 4 × 500 mg

lysed using visual (histogram and probability graphics) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test). Two- and multiple-group comparisons between categorical variables were performed by χ^2 test or by Fisher's exact test. χ^2 test with Bonferroni correction was used for subgroup comparisons. Multiple independent group comparisons were performed using analysis of variance (ANOVA) test for normally distributed numerical variables and using Kruskal-Wallis test for non-normally distributed numerical variables. Comparison of numerical variables between two independent groups was performed using *t*-test for normally distributed variables and using Mann-Whitney *U* test for non-normally distributed variables. The level of significance was determined as $p < 0.05$.

Results

The present study included 166 patients (mean age: 40 ±12 years) with *H. pylori* infection. Of the patients, 68.7% were female, 27.1% were smokers, and 33.7% had a history of NSAID use. The general characteristics of the patients are shown in Table II.

Of the *H. pylori* infections, 144 were in the antrum and 138 were in the corpus. The characteristics according to the localisations (antrum and corpus) are shown in Table III.

Among the patients, 50 (30.1%) were in the LAM-B group, 59 (35.5%) were in the LAM-T group, and 57 (34.3%) were in the LAM-BT group. The general characteristics of the treatment groups are shown in Table IV. The treatment groups were similar in terms of demographic and lesion characteristics. The rate of patients receiving NSAIDs was the lowest in the LAM-BT group. Eradication rates were over 80% and similar in each group. Although statistically not significant, the LAM-BT group had the highest clinical eradication rate at 93%. The rate of adverse events was the highest in the LAM-T group, and no adverse event was observed in the LAM-B group.

Helicobacter pylori eradication was achieved in 143 (86.1%) patients. The characteristics of the patients with and without eradication of *H. pylori* were compared (Table V). No significant difference was determined between the groups in terms of demographic or histopathological features.

Table II. General characteristics of the patients with *H. pylori* infection

Characteristics	Value
Age [years], mean ± SD	40 ±12
Gender, *n* (%):	
Male	52 (31.3)
Female	114 (68.7)
BMI [kg/m^2], *n* (%):	
< 18.5	2 (1.2)
18.5–< 25	58 (34.9)
25–< 30	65 (39.2)
≥ 30	41 (24.7)
Alcohol consumption, *n* (%)	1 (0.6)
Smoking, *n* (%)	45 (27.1)
NSAIDs use, *n* (%)	56 (33.7)
Localization of *H. pylori* infection, *n* (%):	
Antrum	28 (16.9)
Corpus	22 (13.3)
Antrum + corpus	116 (69.9)

SD – standard deviation, BMI – body mass index, NSAIDs – non-steroidal anti-inflammatory drugs.

Table III. Characteristics according to the localisations of *H. pylori*

Parameter	Localisation	
	Antrum (*n* = 144)	Corpus (*n* = 138)
H. pylori load, *n* (%):		
Normal	22 (13.3)	28 (16.9)
Mild	43 (25.9)	50 (30.1)
Moderate	72 (43.4)	70 (42.2)
Marked	29 (17.5)	18 (10.8)
Severity of inflammation, *n* (%):		
Normal	0 (0.0)	1 (0.6)
Mild	41 (24.7)	68 (41.0)
Moderate	83 (50.0)	87 (52.4)
Marked	42 (25.3)	10 (6.0)
Degree of activation, *n* (%):		
Normal	21 (12.7)	35 (21.1)
Mild	38 (22.9)	46 (27.7)
Moderate	90 (54.2)	78 (47.0)
Marked	17 (10.2)	7 (4.2)
Atrophy, *n* (%)	26 (15.7)	5 (3.0)
Metaplasia, *n* (%)	30 (18.1)	3 (1.8)

Table IV. General characteristics of the treatment groups

Parameter	Treatment groups			*P*-value
	LAM-B (*n* = 50)	LAM-T (*n* = 59)	LAM-BT (*n* = 57)	
Age [year], mean ± SD	38 ±10	40 ±12	40 ±13	0.533
Gender, *n* (%):				
Male	12 (24.0)	23 (39.0)	17 (29.8)	0.233
Female	38 (76.0)	36 (61.0)	40 (70.2)	
BMI [kg/m^2], *n* (%):				
< 18.5–24.9	22 (44.0)	21 (35.6)	17 (29.8)	0.210
25.0–29.9	15 (30.0)	21 (35.6)	29 (50.9)	
≥ 30.0	13 (26.0)	17 (28.8)	11 (19.3)	
Alcohol consumer, *n* (%)	0 (0.0)	0 (0.0)	1 (1.8)	–
Smoking, *n* (%)	15 (30.0)	16 (27.1)	14 (24.6)	0.819
NSAIDs use, *n* (%)	25 (50.0)[c]	17 (28.8)	14 (24.6)[a]	0.013
Localisation of lesion, *n* (%):				
Antrum	6 (12.0)	13 (22.0)	9 (15.8)	0.508
Corpus	8 (16.0)	5 (8.5)	9 (15.8)	
Antrum + corpus	36 (72.0)	41 (69.5)	39 (68.4)	
H. pylori load*, median (min.–max.)	2 (1–3)	2 (1–3)	2 (1–3)	0.918
Severity of inflammation*, median (min.–max.)	2 (1–3)	2 (1–3)	2 (1–3)	0.537
Degree of activation*, median (min.–max.)	2 (0–3)	2 (0–3)	2 (1–3)	0.824
Presence of atrophy**, *n* (%)	8 (16.0)	12 (20.3)	10 (17.5)	0.835
Presence of metaplasia**, *n* (%)	9 (18.0)	13 (22.0)	10 (17.5)	0.798
Presence of eradication, *n* (%)	41 (82.0)	49 (83.1)	53 (93.0)	0.180
Presence of adverse event, *n* (%)	0 (0.0)[b]	6 (10.2)[a]	2 (3.5)	0.034

*SD – standard deviation, BMI – body mass index, NSAIDs – non-steroidal anti-inflammatory drugs, min.–max. – minimum–maximum. *The region with higher score was evaluated in the patients with localisation in the antrum + corpus. **The region with change was evaluated in the patients with localisation in the antrum + corpus. [a]Different from the LAM-B group, [b]Different from the LAM-T group, [c]Different from the LAM-BT group.*

Discussions

In recent years the eradication rate of *H. pylori* infection has been gradually decreasing with standard first-line triple therapy [14]. Although an eradication rate of over 90% is still being achieved with seven-day triple therapy options for *H. pylori* infection in regions with low antibiotic resistance, [15] the eradication rate has been reduced to below 80% in regions with the problem of antibiotic resistance [14]. Alternative methods of first-line therapy such as increasing drug dose [16], prolonging treatment period [17], sequential administration of drugs [18], or using different drug combinations [19–21] have emerged to achieve a successful eradication.

In a systematic review with meta-analysis in which studies on first-line therapy in eradicating *H. pylori* infection were evaluated, 14-day sequential treatment, but not 10-day treatment, was concluded to be more effective as compared with triple therapy given for 14 days as first-line treatment [22]. Liou *et al.* [23] determined the eradication rate of *H. pylori* to be 90.4% with bismuth-based first-line quadruple therapy (300 mg of bismuth tripotassium dicitrate four times a day, 30 mg of lansoprazole two times a day, 500 mg of tetracycline four times a day, and 500 mg of metronidazole three

Table V. Characteristics of the patients with and without eradication of *H. pylori*

Parameter	Patients		*P*-value
	Without eradication (*n* = 23)	With eradication (*n* = 143)	
Age [years], mean ± SD	37 ±10	40 ±12	0.220
Gender, *n* (%):			
Male	8 (34.8)	44 (30.8)	0.700
Female	15 (65.2)	99 (69.2)	
BMI [kg/m^2], *n* (%):			
< 18.5–24.9	9 (39.1)	51 (35.7)	0.312
25.0–29.9	6 (26.1)	59 (41.3)	
≥ 30.0	8 (34.8)	33 (23.1)	
Alcohol consumer, *n* (%)	0 (0.0)	1 (0.7)	–
Smoking, *n* (%)	5 (21.7)	40 (28.0)	0.533
NSAIDs use, *n* (%)	6 (26.1)	50 (35.0)	0.403
Localization of *H. pylori*, *n* (%):			
Antrum	1 (4.3)	27 (18.9)	0.213
Corpus	3 (13.0)	19 (13.3)	
Antrum + corpus	19 (82.6)	97 (67.8)	
H. pylori load*, median (min.–max.)	2 (1–3)	2 (1–3)	0.179
Severity of inflammation*, median (min.–max.)	2 (1–3)	2 (1–3)	0.404
Degree of activation*, median (min.–max.)	2 (1–3)	2 (0–3)	0.638
Presence of atrophy**, *n* (%)	5 (21.7)	25 (17.5)	0.571
Presence of metaplasia**, *n* (%)	3 (13.0)	29 (20.3)	0.573
Treatment group, *n* (%):			
LAM-B	9 (39.1)	41 (28.7)	0.180
LAM-T	10 (43.5)	49 (34.3)	
LAM-BT	4 (17.4)	53 (37.1)	
Adverse event, *n* (%)	0 (0.0)	8 (5.6)	0.601

*SD – standard deviation, BMI – body mass index, NSAIDs – non-steroidal anti-inflammatory drugs, min.–max. – minimum-maximum. *The region with higher score was evaluated in the patients with localisation in the antrum + corpus. **The region with change was evaluated in the patients with localisation in the antrum + corpus.*

times a day). The rate of adverse events with that treatment modality was 67%, and the rate of adverse events causing drug discontinuation was 10%. Uygun *et al.* [24] reported the eradication rate to be 82.3% with the same treatment modality. Alboraie *et al.* [25] compared the first-line treatment modality of 10-day triple therapy containing omeprazole, amoxicillin, and clarithromycin with 10-day quadruple therapy containing omeprazole, bismuth, tetracycline, and metronidazole. They found a higher eradication rate with bismuth-based quadruple therapy as compared to clarithromycin-based triple therapy (88% vs. 68.6%). In light of the above-mentioned information, we also achieved an eradication rate of over 80% by implementing bismuth-based (without clarithromycin) treatment regimens sequentially for 14 days. All treatment groups were similar in terms of demographical, clinical, and histopathological features. Although the eradication rate showed no significant difference among the three groups, the highest eradication rate was clinically observed in the LAM-BT group, at 93%. The rate

of adverse events was the highest in the LAM-T group (10.2%). Comparison of the characteristics of patients with and without eradication of *H. pylori* revealed no difference in terms of demographical, clinical, or histopathological features.

There are numerous factors that influence treatment for *H. pylori* eradication. In addition to antibiotic resistance, these factors include personal, genetic, and environmental factors [14]. While some studies have reported gender difference for response to the eradication therapy [25, 26], some have found no difference [27]. In the present study, the eradication rates were not different between males and females. Smoking has also been reported as one of the factors unfavourably influencing eradication [26, 28]. In the present study, the rate of smoking was similar in the patient groups with and without successful eradication.

In gastroduodenal pathology, there is a complex relation between *H. pylori* infection and NSAIDs. Both *H. pylori* infection and nonselective use of NSAIDs have been reported as independent risk factors for peptic ulcer development and ulcer bleeding. These factors probably show additive or synergistic effect, as well [29, 30]. Therefore, clinicians want to test the presence of *H. pylori* and to treat it if present, to reduce development and complications of ulcers in individuals receiving NSAIDs [30]. In the present study, 33.7% of the patients were using NSAIDs. The rate of NSAID use was the lowest (24.6%) in the LAM-BT group, in which the eradication rate was 93%. Nevertheless, no significant difference was found between the groups with and without successful eradication in terms of NSAID use.

In their study, Onal *et al.* [31] investigated the effect of *H. pylori* density, which was determined by histological grading, on the success of eradication therapy and reported that *H. pylori* density negatively affected triple therapy (lansoprazole, clarithromycin, amoxicillin) but not quadruple therapy (colloidal bismuth subcitrate, lansoprazole, tetracycline, metronidazole). Shah *et al.* [32] determined a correlation between *H. pylori* density and complications such as duodenal ulcer, reflux esophagitis, and antral erosions and found a significantly lower eradication rate in the patients with higher *H. pylori* density. In the present study, no significant difference was determined between the patients with and without eradication in terms of graded histopathological features, including *H. pylori* density.

Conclusions

Based on the knowledge that clarithromycin resistance is high in Turkey, the present study tested the combination regimens without clarithromycin as the first-line therapy and achieved an eradication rate of over 80% in all treatment groups with an eradication rate of 93% achieved in the LAM-BT group. Knowing and monitoring the rates of regional antibiotic resistance, which is among the factors that influence eradication, are important to overcome this problem for successful treatment of *H. pylori* infections.

Conflict of interest

The authors declare no conflict of interest.

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