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Comparison of *Helicobacter pylori* Eradication Rates of 2-Week Levofloxacin-Containing Triple Therapy, Levofloxacin-Containing Bismuth Quadruple Therapy, and Standard Bismuth Quadruple Therapy as a First-Line Regimen

Evrim Kahramanoğlu Aksoy[a] Ferdane Pirinçci Sapmaz[a] Zeynep Göktaş[b]
Metin Uzman[a] Yaşar Nazlıgül[a]

[a]Department of Gastroenterology, Keçiören Training and Research Hospital, and [b]Department of Nutrition and Dietetics, Faculty of Health Sciences, Hacettepe University, Ankara, Turkey

Significance of the Study

- This study compared the efficacy of 3 *Helicobacter pylori* eradication regimens, 2 of which contained levofloxacin, as the first line of treatment. Both quadruple regimens (standard bismuth quadruple therapy or levofloxacin-containing bismuth quadruple therapy) were highly effective in eradicating the infection and significantly superior to levofloxacin-containing triple therapy. Quadruple therapies should be used as first-line therapy for *H. pylori* infection.

Keywords

Helicobacter pylori infection · Bismuth-containing quadruple therapy · Levofloxacin-containing triple therapy · Eradication rate

Abstract

Objective: The aim of this study was to compare the efficacy and safety of 2-week levofloxacin-containing triple therapy, levofloxacin-containing bismuth quadruple therapy, and standard bismuth-containing quadruple therapy as a first-line regimen for the eradication of *Helicobacter pylori*. ***Methods:*** A total of 329 patients with *H. pylori* infection were randomly divided into 3 groups to receive one of the following regimens: (a) levofloxacin-containing bismuth quadruple therapy, RBAL (rabeprazole 20 mg, b.i.d., bismuth subsalicylate 562 mg, b.i.d., amoxicillin 1 g, b.i.d, levofloxacin 500 mg, once daily), (b) standard bismuth quadruple therapy, RBMT (rabeprazole 20 mg, b.i.d, subsalicylate 562 mg, b.i.d., metronidazole 500 mg, t.i.d, tetracycline 500 mg, q.i.d), or (c) levofloxacin-containing triple therapy, RAL (rabeprazole 20 mg, b.i.d., amoxicillin 1 g, b.i.d, levofloxacin 500 mg, once daily). The primary outcome was the eradication rate in the intention-to-treat (ITT) and per protocol (PP) analysis. ***Results:*** The eradication rates of the above 3 groups using ITT analysis were RBAL 83.8%, RBMT 88.3%, and RAL 74.8% compared with 91.2, 92.5, and 79.2%, respectively, using PP analysis. The eradication rate using RBMT was significantly higher than that of RAL ($p = 0.029$ in ITT analysis and $p = 0.017$ in PP analysis). Several side effects occurred in 156 patients (54.1%)

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E-Mail karger@karger.com
www.karger.com/mpp

Evrim Kahramanoğlu Aksoy, MD
Department of Gastroenterology, Keçiören Training and Research Hospital
Pınarbaşı Mah., Sanatoryum Caddesi Ardahan Sokak D: 25
TR–06280 Keçiören, Ankara (Turkey)
E-Mail evrims1979@yahoo.com

in the RBAL group, 215 (52.3%) in the RBMT group, and 56 (26.2%) in the RAL group ($p > 0.05$, RBAL vs. RBMT; $p < 0.001$, RBMT vs. RAL; $p < 0.001$, RBAL vs. RAL). ***Conclusion:*** All bismuth-containing quadruple therapies had acceptable eradication rates, but levofloxacin-containing triple therapy was not as good as quadruple therapies. Hence, quadruple therapies should be considered the preferred first-line therapy for *H. pylori* infections.

Introduction

Despite the fact that the presence of *Helicobacter pylori* and the diseases it causes, such as gastroduodenal ulcers, gastritis, gastric adenocarcinoma, mucosa-associated lymphoid tissue lymphoma, and nonulcer dyspepsia, have been known for over 30 years, treatment option(s) remain a challenge [1, 2]. Eighty percent of the population in developing countries and 20–50% of the population in the developed countries are estimated to carry this pathogen [3]. Eradication of *H. pylori* infection has been recommended as an effective approach for curing or preventing these *H. pylori*-associated diseases [4]. Standard triple therapy no longer provides the targeted treatment success. In countries with 25–30% clarithromycin resistance, the eradication rates declined significantly from 90 to 60–70% in 2006 [5, 6]. Although there might be many reasons for the decrease of efficacy of standard triple therapy, such as compliance, bacterial load, host CYP2C19 polymorphisms, and gastric acidity, the most important reason is the increase in *H. pylori* resistance to clarithromycin [7, 8].

In high (>15%) clarithromycin resistance areas, bismuth quadruple or nonbismuth quadruple concomitant therapies are recommended [9]. In regions of high (>15%) dual clarithromycin and metronidazole resistance (>40%), bismuth-containing quadruple therapies are the treatment of choice [9]. Although metronidazole resistance in Europe has stabilized at 34.9% of *H. pylori* isolates, and the eradication rate can be improved by prolonging the duration of treatment from 10 to 14 days, some studies have shown inefficacy of these treatments [8, 10]. Based on the recent systematic review of the prevalence (from 1999 to 2015) of primary antibiotic resistance of *H. pylori* strains in different geographical regions of Turkey, the overall primary antibiotic resistance rates of *H. pylori* strains were as follows: amoxicillin 0.971%, clarithromycin 24.864%, metronidazole 33.747%, tetracycline 3.511%, and levofloxacin 23.769%. There was an increase in primary resistance rates to clarithromycin and metronidazole in different years [11].

Levofloxacin is a fluoroquinolone with a broad spectrum of activity both against gram-positive and gram-negative bacteria [12]. The efficacy of levofloxacin-containing triple therapy as second- and third-line therapy has been shown in various studies [12, 13]. Furthermore, there are studies showing levofloxacin-containing triple therapy as an effective first-line treatment [14, 15]. There are controversial data in comparing the efficacy and duration of bismuth-containing quadruple therapies and levofloxacin-containing triple therapies [16, 17]. Some studies showed the efficacy of 1-week bismuth- and levofloxacin-containing quadruple therapies for first-line therapy. However, in other studies the ineffectiveness of these treatment regimens as second-line therapy were pointed out [16, 17].

Therefore, in this study, the aim was to determine the efficacy, side effects, and tolerability of a 2-week levofloxacin-containing triple therapy, levofloxacin-containing bismuth quadruple therapy, and standard bismuth-containing quadruple therapy as a first-line regimen in Turkey.

Subjects and Methods

Study Population

A total of 329 patients infected with *H. pylori* were enrolled in this prospective, open-label, randomized study conducted at the Gastroenterology Outpatient Clinic, Keçiören Training and Research Hospital, Ankara, Turkey, from October 2016 to April 2017. The *H. pylori* infection was diagnosed by histological analysis (2 samples from the antrum and 1 sample from the corpus) using Giemsa and hematoxylin and eosin stainings. Patients (aged between 18 and 70 years) who underwent endoscopy due to recurrent dyspeptic symptoms (epigastric pain, epigastric fullness, epigastric dullness, nausea, vomiting, quick saturation) or alarm symptoms and tested positive for *H. pylori*, and who were not previously treated for *H. pylori* infection, were included in the study. Exclusion criteria were H_2 receptor antagonists, bismuth preparations, proton pump inhibitors, and antibiotic use up to 4 weeks before upper endoscopy, malignant or severe disease, gastric surgery, pregnant or lactating women, and known allergy to antibiotics.

The study protocol was approved by the Institutional Ethics Committee, and the study was performed in accordance with good clinical practice and the Declaration of Helsinki. Written informed consent was obtained from each participant.

Treatment Protocols

Random allocation of patients to 3 treatment groups (using a random-numbers table) was done by a gastroenterologist (E.K.A.) to receive one of the following regimens: (a) levofloxacin-containing bismuth quadruple therapy, RBAL (rabeprazole 20 mg, b.i.d., bismuth subsalicylate 562 mg, b.i.d., amoxicillin 1 g, b.i.d, levoflox-

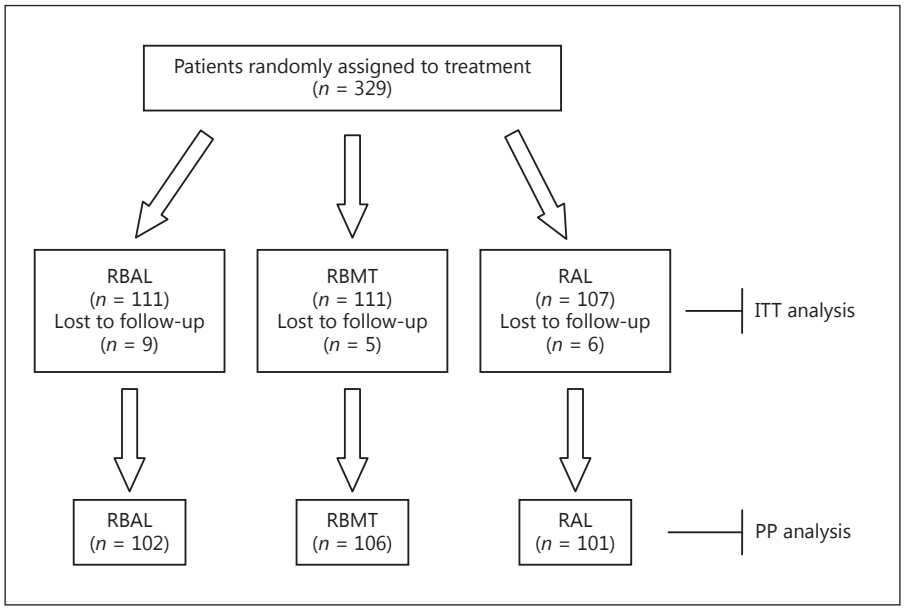

Fig. 1. Flow diagram of the study. RBAL, rabeprazole 20 mg, b.i.d., bismuth subsalicylate 562 mg, b.i.d., amoxicillin 1 g, b.i.d, levofloxacin 500 mg, once daily; RBMT, rabeprazole 20 mg, b.i.d, subsalicylate 562 mg, b.i.d., metronidazole 500 mg, t.i.d, tetracycline 500 mg, q.i.d.; RAL, rabeprazole 20 mg, b.i.d., amoxicillin 1 g, b.i.d, levofloxacin 500 mg, once daily; ITT, intention-to-treat; PP, per protocol.

Table 1. Baseline demographic and endoscopic data

	RBAL	RBMT	RAL	*p* value
Patients (ITT)	111	111	107	>0.05
Gender (male/female)	37/64	45/56	42/59	>0.05
Age, years	49.1±14.54	45.3±12.71	47.9±13.99	>0.05
Smoking habit (yes/no)	27/74	24/77	25/76	>0.05
Endoscopic diagnosis				
Gastritis	109 (98.2)	107 (96.4)	107 (100)	>0.05
Gastric ulcer	2 (1.8)	6 (5.4)	1 (0.9)	>0.05
Duodenal ulcer	5 (4.5)	10 (9.0)	2 (1.9)	>0.05
Esophagitis	10 (9.0)	9 (8.1)	4 (3.7)	>0.05
Duodenitis	27 (24.3)[a]	31 (27.9)[a]	11 (10.3)[b]	0.006, 0.001*

Data are presented as *n* (%) or mean ± SD, as appropriate. RBAL, rabeprazole 20 mg, b.i.d., bismuth subsalicylate 562 mg, b.i.d., amoxicillin 1 g, b.i.d, levofloxacin 500 mg, once daily; RBMT, rabeprazole 20 mg, b.i.d, subsalicylate 562 mg, b.i.d., metronidazole 500 mg, t.i.d, tetracycline 500 mg, q.i.d.; RAL, rabeprazole 20 mg, b.i.d., amoxicillin 1 g, b.i.d, levofloxacin 500 mg, once daily; ITT, intention-to-treat. * $p = 0.006$, RBAL vs. RAL; $p = 0.001$, RBMT vs. RAL; $p > 0.05$, RBAL vs. RBMT. [a, b] Protocols within a row without a common superscript differ.

acin 500 mg, once daily, for 2 weeks) ($n = 111$ patients), (b) standard bismuth-containing quadruple therapy, RBMT (rabeprazole 20 mg, b.i.d, subsalicylate 562 mg, b.i.d., metronidazole 500 mg, t.i.d, tetracycline 500 mg, q.i.d, for 2 weeks) ($n = 111$ patients), or (c) levofloxacin-containing triple therapy, RAL (rabeprazole 20 mg, b.i.d., amoxicillin 1 g, b.i.d, levofloxacin 500 mg, once daily, for 2 weeks) ($n = 107$ patients). *H. pylori* eradication was determined using the stool antigen test with an enzyme immunoassay utilizing a monoclonal antibody. The test was performed at least 4 weeks after the end of therapy. Patients were asked to avoid antacid treatment and antibiotics for 1 month before the stool antigen test.

A questionnaire was used to record side effects for all patients. In the RBAL group, 106 of 111 patients completed the course and 5 patients failed to take at least 75% of the drugs. In the RBMT group, 102 of 111 patients completed the course and 9 patients failed to take at least 75% of the drugs. In the RAL group, 101 of 107 patients completed the course and 6 patients failed to take at least 75% of the drugs. Twenty patients (5 in RBAL, 9 in RBMT, and 6 in RAL therapy groups) withdrew from the treatment due to nausea, dysphagia, drowsiness, insomnia, headache/dizziness, chest pain, and skin allergy. A flow diagram of the study is presented in Figure 1.

Table 2. *Helicobacter pylori* eradication rates with different treatment regimens

	RBAL	RBMT	RAL	*p* value
ITT analysis	93/111 (83.8)[a, b]	98/111 (88.3)[a]	80/107 (74.8)[b]	0.029*
95% CI	76.9–90.7	82.3–94.2	72.7–76.9	
Per protocol analysis	93/102 (91.2)[a, b]	98/106 (92.5)[a]	80/101 (79.2)[b]	0.017**
95% CI	85.7–96.7	87.5–97.5	71.3–87.1	
Compliance	106/111 (95.5)	102/111 (91.9)	101/107 (94.4)	>0.05
95% CI	91.6–99.4	86.8–96.9	90.1–98.8	

Data are presented as *n* (%) with 95% CI. See Table 1 footnote for abbreviations. * $p = 0.029$, RBMT vs. RAL; $p > 0.05$, RBAL vs. RBMT; $p > 0.05$, RBAL vs. RAL. ** $p = 0.017$, RBMT vs. RAL; $p > 0.05$, RBAL vs. RBMT; $p > 0.05$, RBAL vs. RAL. [a, b] Protocols within a row without a common superscript differ.

Statistical Analysis

Statistical analyses were performed using the computer program Statistical Package for the Social Sciences (SPSS), version 22.0 (IBM, Armonk, NY, USA). The Levene test was used to test for equality of variances between arms. One-way ANOVA was used for comparison of more than 2 group means. The χ^2 test was used to compare eradication rates, side effects, and symptoms between different treatment groups. In the assessment of treatment, intention-to-treat (ITT) and per protocol (PP) analyses were used. All of the participants were included in the ITT analysis. Participants who did not follow the study protocol or dropped out of the study were excluded from the PP analysis. Data are presented as the mean ± standard deviation or number and percentage. Differences were considered significant at $p < 0.05$.

Results

Demographic Data

Relevant demographic and endoscopic data are given in Table 1. There was no difference between groups in terms of age, sex, and smoking habits ($p > 0.05$).

Eradication Rates

The efficacy of the eradication regimens is shown in Table 2. In the ITT analysis, eradication rates were 93/111 (83.8%; 95% CI, 76.9–90.7) with RBAL, 98/111 (88.3%; 95% CI, 82.3–94.2) with RBMT, and 80/107 (74.8%; 95% CI, 72.7–76.9%) with RAL. In the PP analysis, eradication rates were 93/86 (91.2%; 95% CI, 85.7–96.7%) with RBAL, 98/106 (92.5%; 95% CI, 87.5–97.5%) with RBMT, and 80/101 (79.2%; 95% CI, 71.3–87.1%) with RAL.

In the comparison of all treatment groups separately with each other based on *H. pylori* eradication rates, there were statistically significant differences between the RBMT and RAL groups for both ITT and PP analyses ($p = 0.029$ and $p = 0.017$, respectively) (Table 2). There were no statistically significant differences between RBAL and RBMT or between RBAL and RAL groups in terms of eradication rates ($p > 0.05$) (Table 2).

Side Effects

The most common side effects were darkened stool, nausea, abdominal pain, black tongue, and diarrhea. Several side effects at various degrees occurred in 156 patients (54.1%) in the RBAL group, 215 (52.3%) in the RBMT group, and 56 (26.2%) in the RAL group ($p > 0.05$, RBAL vs. RBMT; $p < 0.001$, RBMT vs. RAL; $p < 0.001$, RBAL vs. RAL) (Table 3).

Discussion

This study showed that both quadruple regimens (standard bismuth quadruple therapy and levofloxacin-containing bismuth quadruple therapy) were highly effective in eradicating the infection (>90%), and better than levofloxacin-containing triple therapy (79.2%), in Turkey, which has one of the highest levels of primary clarithromycin resistance (48.2%) [18].

The high eradication rates of RBAL (91.2%) and RBMT (92.5%) are consistent with the recommendation of the current guidelines that bismuth-containing quadruple therapies be used as first-line treatment in areas with high resistance to clarithromycin (>15%) [9, 19]. Bismuth salts act topically, and less than 1% of the oral dose is absorbed. In acidic pH it forms nonsoluble polymers. In this cytoprotective form, it covers the ulcer crater and prevents it from gastric acidity. Furthermore, it possess antibacterial effects by inhibiting various enzymes produced by *H. py-*

Table 3. Side effects of different treatment regiments

	RBAL	RBMT	RAL	*p* value*		
Side effects of treatment (yes), %	54.1[a]	52.3[a]	26.2[b]	>0.05	<0.001	<0.001
Patients withdrawn due to side effects	5 (4.5)	9 (8.1)	6 (5.6)	>0.05	>0.05	>0.05
Side effects						
Nausea	37 (33.3)[a]	45 (40.5)[a]	13 (12.1)[b]	>0.05	<0.001	<0.001
Vomiting	6 (5.4)[a]	11 (9.9)[a]	0 (0.0)[b]	>0.05	<0.001	0.015
Metallic taste	0 (0.0)[a]	23 (20.7)[b]	0 (0.0)[a]	<0.001	<0.001	>0.05
Itchiness	8 (7.2)	6 (5.4)	5 (4.7)	>0.05	>0.05	>0.05
Skin rash	5 (4.5)	4 (3.6)	7 (6.5)	>0.05	>0.05	>0.05
Constipation	0 (0.0)	1 (0.9)	0 (0.0)	>0.05	>0.05	>0.05
Diarrhea	14 (12.6)[a]	4 (3.6)[b]	13 (12.1)[a]	0.014	0.019	>0.05
Dysphagia	1 (0.9)[a]	21 (18.9)[b]	0 (0.0)[a]	<0.001	>0.001	>0.05
Chest pain	1 (0.9)[a]	9 (8.1)[b]	0 (0.0)[a]	0.010	0.003	>0.05
Darkened stool	47 (42.3)[a]	51 (45.9)[a]	0 (0.0)[b]	>0.05	<0.001	<0.001
Black tongue	12 (10.8)[a]	27 (24.3)[b]	0 (0.0)[c]	0.08	>0.001	<0.001
Vaginal discharge	5 (4.5)	1 (0.9)	5 (4.7)	>0.05	>0.05	>0.05
Headache	7 (6.3)	1 (0.9)	4 (3.7)	>0.05	>0.05	>0.05
Abdominal pain	13 (11.7)	11 (9.9)	9 (8.4)	>0.05	>0.05	>0.05

Data are presented as *n* (%) unless otherwise indicated. See Table 1 footnote for abbreviations. * Three *p* values were used for 3 comparisons: RBAL vs. RBMT, RBMT vs. RAL, and RBAL vs. RAL, respectively. [a, b, c] Protocols within a row without a common superscript differ.

lori (including urease, catalase, and lipase/phospholipase), preventing adhesion of *H. pylori* to surface epithelial cells, and inhibiting ATP synthesis and some membrane functions in *H. pylori* [20–22]. It has been reported that the addition of bismuth to standard triple therapy improved the eradication rate [23, 24]. Equally important, Molina-Infante et al. [25] have reported that 2 non-bismuth quadruple therapies were effective in eradicating more than 90% of *H. pylori* infections in areas with a high clarithromycin resistance rate.

Levofloxacin, a broad-spectrum fluoroquinolone, was used in triple, quadruple, and sequential treatments [12–17, 26, 27] in which higher eradication rates of levofloxacin- than clarithromycin-containing therapy were found when used in a triple first-line regimen (7–10 days) [14, 15, 17]. In the present study, levofloxacin was used in triple and bismuth-containing quadruple therapies for 2 weeks, and triple therapy did not eradicate *H. pylori*. However, it has previously been shown that five days of levofloxacin-containing quadruple concomitant therapy was as effective and safe in eradicating *H. pylori* infection as 10 days of levofloxacin-containing sequential therapy [28]. Also, it has been reported that levofloxacin-containing sequential therapy is more effective than clarithromycin-containing sequential therapy [29].

There are controversial findings on the efficacy of levofloxacin-containing treatments (with or without bismuth) compared with standard bismuth quadruple treatment as first- or second-line treatments. In a study from Hong Kong, levofloxacin-containing bismuth quadruple therapy was inferior to standard bismuth quadruple therapy in the treatment of resistant *H. pylori* infection (ITT eradication rates of 73 and 88% and PP eradication rates of 78 and 94%, respectively, $p = 0.030$). For those with a previous history of levofloxacin triple therapy, the eradication rates were 71 and 93%, respectively ($p = 0.139$) [16].

The high eradication rates of RBAL (91.2%) and RBMT (92.5%) are consistent with those of Su et al. [17], who reported an eradication rate of 89.66% with levofloxacin-containing bismuth quadruple therapy, which was better than clarithromycin-containing bismuth quadruple therapy (80.25% eradication rate) and levofloxacin-containing triple therapy (81.93% eradication rate).

In this study, the eradication rate of levofloxacin-containing triple therapy of less than 80% seemed to indicate that this was not a good option for first-line treatment.

However, the addition of bismuth to the triple therapy improved the success rate to over 90%. Since it is not possible to overcome levofloxacin resistance by increasing the dose and duration of the drug, standard quadruple therapy would seem to be the best choice as first-line treatment as an empiric protocol, with an eradication rate over 90%.

In this study, considering the stable increase in levofloxacin and metronidazole resistance and negligible tetracycline resistance, quadruple therapies with bismuth seemed to be the best first-line treatment for *H. pylori* eradication in Turkey. However, the standard bismuth quadruple therapy caused side effects, but withdrawal rates were similar between the 3 groups. Also, the present study suggests that 14-day levofloxacin plus bismuth quadruple therapy can be used empirically in places where the levofloxacin resistance is known to be low. Further larger, multicenter studies with susceptibility test are needed to compare the eradication rates, and also compliance rates, of levofloxacin-containing bismuth quadruple therapy and levofloxacin-containing concomitant and sequential therapies with other treatment regimens.

The main limitation of our study is that no culture for *H. pylori* was performed and, therefore, antibiotic susceptibility/resistance rates were unknown.

Conclusion

All bismuth-containing quadruple therapies had higher eradication rates than levofloxacin-containing triple therapy. Hence, standard bismuth quadruple therapy should be considered the preferred first-line therapy if the antibiotic susceptibility is not known.

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