Clarithromycin *versus* levofloxacin-based regimens for *Helicobacter pylori* eradication in the Kurdistan Region of Iraq: A randomized clinical trial

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Abstract

Helicobacter pylori infection is a predisposing factor for gastric cancer. This prospective, randomized clinical trial aimed to compare *H. pylori* eradication rates associated with a clarithromycin-based regimen and levofloxacin-based regimen. *H. pylori* infection was confirmed by a rapid urease test during endoscopy and its eradication by a urea breath test. In this study, 192 patients were recruited; 93 patients received a clarithromycin-based regimen and 99 a levofloxacin-based regimen. Sixty-four patients completed the clarithromycin-based regimen and 60 the levofloxacin-based regimen. The eradication success rate of the clarithromycin-based regimen was 52/64 (81.25%), while that of the levofloxacin-based regimen was 49/60 (81.6%) (P=0.9524; odds ratio [OR]=1.0280; confidence interval [CI]=0.4153-2.5447). Investigation of the risk factors associated with treatment failure showed that the overall efficacy of the regimens was influenced by body mass index (BMI), with a high failure rate observed in patients with a high BMI (P=0.0174; OR=1.1116; CI=1.0187-1.2129). Age, sex, endoscopic diagnosis and smoking did not influence treatment outcomes. Further studies are needed to monitor *H. pylori* antibiotic resistance rates.

Introduction

Helicobacter pylori is a Gram-negative microaerophilic bacterium,[1] the discovery of which changed the mainstream understanding of gastric diseases, particularly peptic ulcer.[1] Infection with *H. pylori* predisposes one to gastric cancer – the third most commonly occurring cause of cancer-related death.[2] A total of 50% of the world's population has *H. pylori* infection,[3] with a prevalence rate of 20% in developed countries and 80% in developing countries.[3] While several regimens have been considered for *H. pylori* eradication, the failure rates associated with eradication are high, varying across countries. With the increased prevalence of antibiotic resistance, *H. pylori* eradication represents a challenge. Different variables such as patient characteristics, underlying disease presence and environmental factors also play an important role in treatment failure. Triple therapy, comprising amoxicillin and clarithromycin plus a proton pump inhibitor, is the most commonly used first-line regimen recommended for the eradication of *H. pylori*.[4] However, owing to increases in the rates of *H. pylori* resistance to clarithromycin, the efficacy of this regimen has been progressively decreasing.[4] Levofloxacin – a fluoroquinolone – was then proposed as an effective and safe second-line medication for the eradication of this bacterium.[5] In a study conducted in Iraq that used molecular methods to detect both clarithromycin and levofloxacin resistance, 16.2% of the strains were resistant to clarithromycin, while 4% were resistant to levofloxacin.[6] No study in Iraq has investigated the eradication success rates associated with the clarithromycin and levofloxacin-based regimens. This study was conducted to investigate the eradication success rate of these two regimens and identify the risk factors associated with *H. pylori* eradication failure.

Materials and Methods

Study design and patients

We conducted a prospective, randomized clinical trial between July 2018 and March 2019 at the Gastrointestinal Disease Center of the Azadi Teaching Hospital, Duhok, Kurdistan Region of Iraq. Patients' *H. pylori* infection status was confirmed using a rapid urease test during endoscopy. The inclusion criteria for patient recruitment were: *H. pylori*-positivity, age 18 years and older, and provision of consent for recruitment. Exclusion criteria included: prior antibiotic use, age younger than 18 years, pregnancy, and the absence of consent for participation. At the end of the study, eradication success rate was determined using intention-to-treat and per-protocol analyses.

Intervention

Participants were randomly allocated to two groups by computer-generated assignment. Recruited patients received either: i) clarithromycin-based triple therapy, comprising clarithromycin 500 mg administered twice daily after meals plus omeprazole 20 mg twice daily before meals, and amoxicillin 1 g twice daily after meals for 14 days; ii) levofloxacin-based triple therapy, comprising levofloxacin 500 mg administered once a day after meals plus omeprazole 20 mg twice daily before meals and amoxicillin 1 g twice daily after meals for 14 days.

Participants were interviewed and provided instructions on how to take the drugs correctly.

The primary outcome of our project was *H. pylori* eradication. All participants were invited to undergo a 14C-urea breath test,

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Contributions: the research was conducted by SAM and supervised by OQBA and NRH. The research project was designed by SAM, OQBA and NRH. The ethical approval was obtained by SAM. Data collection was done by SAM, EGD (esophagogastroduodenoscopy) was performed by RSH and LSA; patients were followed-up by SAM, RSH and LSA. OQBA and NRH contributed in the statistical analysis. All the authors read and approved the final manuscript.

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four weeks after treatment completion. During the test, patients were given a capsule containing 37 kBq (1 μCi) 14-carbon urea, with 20 mL lukewarm water after at least 5 hours of fasting. At 3 min post-dose, the patients consumed 20 mL of lukewarm water. At 10 min post-dose, they were asked to take a deep breath, hold it for approximately 5-10 sec, and then exhale into a breath-card (Heliprobe, Kibion).

The secondary outcomes were compliance and side effects. All participants were instructed to report any side effects associated with medication intake. Patients were instructed on medication use and provided a date for the confirmation of *H. pylori* eradication. All patients were contacted by a pharmacist one week after drug administration initiation and at the end of the treatment period. Drug compliance and adverse events were evaluated by a pharmacist.

Statistics

The eradication rate associated with each regimen was calculated as the percentage of participants with a negative urea breath test among patients who completed the treatment course. Chi-square and Fisher's exact tests were used to compare dichotomous data, and regression analyses were utilized for numerical data. The SPSS 21.0 statistical software (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Ethics

The research proposal was approved by the ethics committee of the College of Pharmacy, and the ethics unit in the Directorate of Health, Duhok, Kurdistan Region of Iraq. Consent was obtained from all participants.

Results

Patient characteristics, compliance, and side effects

We recruited 192 patients who visited Azadi Teaching Hospital's Gastrointestinal Disease Center. The average age of the patients was 37.5±14.3 (Table 1). Of the total patients, 93 received the clarithromycin-based regimen while 99 received the levofloxacin-based regimen. In the clarithromycin group, three patients could not complete the treatment course due to severe gastrointestinal side effects; in the levofloxacin group, no cases of treatment discontinuation were reported due to the severity of adverse effects (Figure 1). All patients except for those who were lost to follow-up and those who could not tolerate the regimen were assessed using the 14Carbon urea breath test after treatment conclusion. Overall, 124 patients completed the treatment course: 64 in the clarithromycin group and 60 in the levofloxacin group. Regarding side effects in the patients with treatment course completion, 55/64 (85.93%) of those in the clarithromycin group developed side effects compared to the 4/60 (6.6%) in the levofloxacin group (Fisher's exact test, P=0.001).

H. pylori eradication rates

A total of 124 patients were involved in the analysis of *H. pylori* eradication rates. The average age of the recruited participants was 37.3±14.2 years. Of them, 48 (38.7%) were male and 77 (61.3%) were female. While the eradication success rate in the clarithromycin-based regimen was 52/64 (81.25%), that in the levofloxacin-based regimen was 49/60 (81.6%) (P=0.9524; odds ratio [OR]=1.0280; confidence interval [CI]=0.4153-2.5447).

Table 1. Characteristics of the participants.

Features	OAC	OAL	Total
BMI (mean ± SD) kg/m^2	26.06±5.4	25.74±4.7	25.9±5.06
Age (mean ± SD) y	37.3±14.2	37.68±14.9	37.5±14.3
Sex			
Male no. (%)	45 (56.96%)	34 (43.03%)	79
Female no. (%)	48 (42.5%)	65 (57.5%)	113
Endoscopic diagnosis			
PUD no. (%)	18 (41.9%)	25 (58.1%)	43
None PUD no. (%)	75 (50.3%)	74 (49.7%)	149
Smoking no. (%)	24 (61.5%)	15 (38.5%)	39
Side effects no. (%)	55 (85.93%)	4 (6.6%)	59
Successful course completion no. (%)	(64/93) 68.8%	(60/99) 60.6%	124

OAC, clarithromycin 500 mg administered twice daily after meals plus omeprazole 20 mg twice daily before meals, and amoxicillin 1 g twice daily after meals for 14 days; OAL, levofloxacin 500 mg once a day after meals plus omeprazole 20 mg twice daily before meals, and amoxicillin 1 g twice daily after meals for 14 days; BMI, body mass index; SD, standard deviation; no., number of patients; (%), percentage of patients; PUD, peptic ulcer disease.

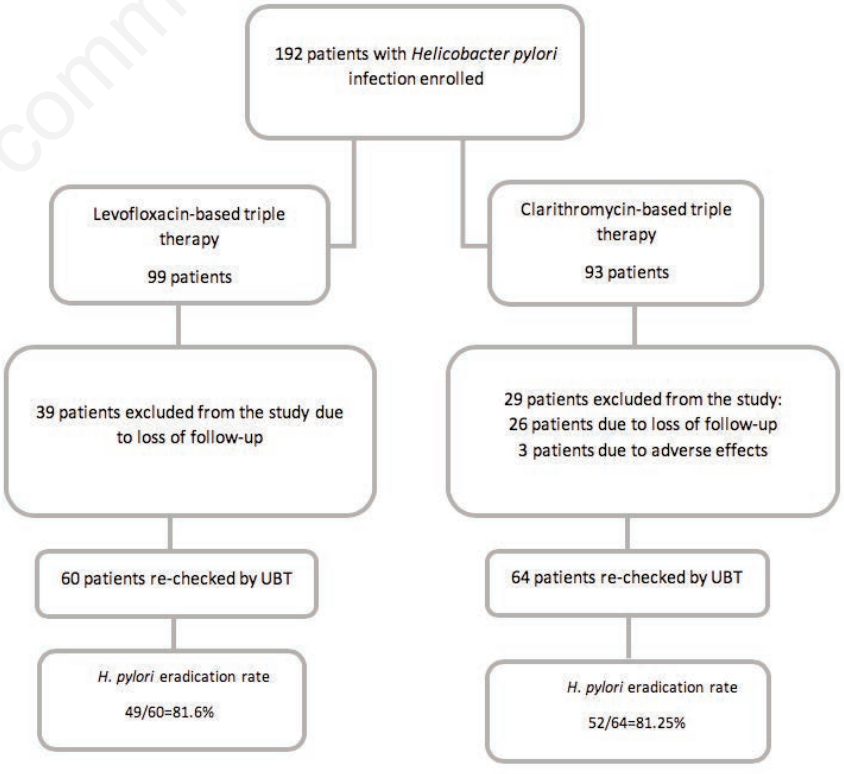

Figure 1. Study flow diagram. UBT, 14C-urea breath test.

Factors associated with failure

First, we studied the risk factors for failure in terms of overall eradication in both regimens. The overall efficacy of the regimens was influenced by the body mass index (BMI), with high failure rates observed in patients with a high BMI (P=0.0174; OR=1.1116; CI=1.0187-1.2129) (Table 2).

The efficacy of either regimen was not influenced by sex, age, smoking and endoscopy diagnosis. We further classified our patients into two groups, by regimen. Then, we compared the subgroups of patients to investigate the effects of different factors on individual regimens. Treatment outcomes in the clarithromycin-based regimen were influenced by BMI, with high failure rates observed in those with a high BMI (Table 3).

Other factors did not show any effects on the eradication rate. Regarding the levofloxacin-based regimen, BMI, age, sex, smoking and endoscopy diagnosis did not influence outcomes (Table 4).

Discussion

H. pylori infection occurs commonly in Iraq,[7] with a prevalence rate of around 80% in the adult population.[8] This infection is associated with peptic ulcer disease and gastric carcinoma.[9] The treatment of *H. pylori* infection using successful eradication methods may improve the clinical outcomes of patients.[1] However, the antibiotic-resistance of *H. pylori* has been increasing progressively, resulting in high eradication failure rates.[10] Antibiotic resistance is markedly recognized in developing countries.[10] Therefore, to choose appropriate antibiotics regimens for the treatment of *H. pylori*, continuous monitoring of antibiotic sensitivity patterns is mandatory. As the clar-

Table 2. Risk factors for *Helicobacter pylori* eradication failure.

Factor	Success	Failure	P-value	OR	CI
BMI (mean ± SD) kg/m^2	25.6±5.1	28.6±5.3	0.017*	1.1	1.018 1.212
Age (mean ± SD) y	37.4±15.06	36.9±9.9	0.9	0.96	0.9660-1.0302
Smoking no. (%)	21 (80.7%)	5 (19.3%)	0.9	1.05	0.3518-3.1828
Sex					
Male no. (%)	42 (87.5%)	6 (12.5%)	0.17	0.5	0.18-1.3631
Female no. (%)	59 (77.6%)	17 (22.4%)			
Endoscopy					
PUD no. (%)	27 (93.1%)	2 (6.9%)	0.08	0.26	0.057-1.1885
None-PUD no. (%)	74 (77.9%)	21 (22.1%)			

OR, odds ratio; CI, confidence interval; BMI, body mass index; SD, standard deviation; no., number of patients; (%), percentage of patients; PUD, peptic ulcer disease. Statistical test (biochemical logistic regression). *Significance set at P<0.05.

Table 3. Risk factors for of *Helicobacter pylori* eradication failure in the clarithromycin-based regimen.

Factor	Success	Failure	P-value	OR	CI
BMI (mean ± SD) kg/m^2	25.99±4.96	29.9±6.5	0.038*	1.14	1.0074-1.2949
Age (mean ± SD) y	38.42±14.81	37.33±12.6	0.8	0.99	0.9512-1.0399
Smoking no. (%)	15 (88.2%)	2 (11.8%)	0.4	0.49	0.0964-2.5240
Sex					
Male no. (%)	26 (89.6%)	3 (10.4%)	0.12	0.33	0.0810-1.3724
Female no. (%)	26 (74.3%)	9 (25.7%)			
Endoscopy					
PUD no. (%)	13 (86.7%)	2 (13.3%)	0.54	0.6	0.1161-3.1018
None-PUD no. (%)	39 (79.6%)	10 (20.4%)			

OR, odds ratio; CI, confidence interval; BMI, body mass index; SD, standard deviation; no., number of patients; (%), percentage of patients; PUD, peptic ulcer disease. Statistical test (logistic regression). *Significance set at P<0.05.

Table 4. Risk factors for *Helicobacter pylori* eradication failure in the levofloxacin-based regimen.

Factor	Success	Failure	P-value	OR	CI
BMI (mean ± SD) kg/m^2	25.22±5.3	27.3±3.5	0.23	1.08	0.9515-1.2283
Age (mean ± SD) y	36.30±15.4	36.5±6.6	0.97	1	0.9553-1.0483
Smoking no. (%)	6 (66.7%)	3 (33.3%)	0.22	2.7	0.5546-13.0223
Sex					
Male no. (%)	16 (84.2%)	3 (15.8%)	0.73	0.77	0.1805-3.3139
Female no. (%)	33 (80.5%)	8 (19.5%)			
Endoscopy					
PUD no. (%)	14 (100%)	0 (0.0%)	0.053	1	0.99-1.1
None-PUD no. (%)	35 (76%)	11 (24%)			

OR, odds ratio; CI, confidence interval; BMI, body mass index; SD, standard deviation; no., number of patients; (%), percentage of patients; PUD, peptic ulcer disease. Statistical test (logistic regression).

ithromycin-based regimen is generally used as a first-line regimen for the eradication of *H. pylori*,[4] the associated resistance rate has been studied thoroughly. In Turkey, the clarithromycin resistance rate ranges from 16.4% to 48.2%[11] while in Iran, it ranges from 1.4% to 26.5%.[12] In Saudi Arabia, the clarithromycin resistance rate was 21%,[13] while in Iraq, the value was 16.2%.[6] Owing to increases in the rates of clarithromycin resistance, levofloxacin was considered as a salvage treatment for *H. pylori* eradication;[5] however, several reports have shown strong resistance to levofloxacin. In a study conducted in Iran, the levofloxacin resistance rate was higher than 20%, while in Iraq, the value was 4%. In our study, the eradication success rate of the clarithromycin-based regimen was 81.25%, which was almost similar to that of the levofloxacin-base regimen (81.6%). This indicates that both regimens can be used in the Kurdistan Region of Iraq, particularly owing to the low side effect rate reported in the study. However, as the clarithromycin-based regimen was associated with higher rates of side effects, the levofloxacin-based regimen can be used as the first line of treatment. Additionally, continuous monitoring is mandatory for the investigation of the trends of antibiotic resistance. In a large multicenter project recruiting patients from a center in Egypt and two centers in Saudi, which compared the clarithromycin and levofloxacin-based regimens, the eradication rates were 78.6% and 84.7%, respectively.[14] In a study conducted in Iran, the *H. pylori* eradication rate in patients receiving the clarithromycin-based regimen was 51.7%, which was lower than that associated with the levofloxacin-based regimen (75%).[15] In another study conducted in China, the *H. pylori* eradication rate associated with the clarithromycin triple regimen was 75% *vs* the eradication rate of 83% for the levofloxacin-based regimen.[16] In a study conducted in India that recruited patients with peptic ulcer perforation, the *H. pylori* eradication rate was 79% in the clarithromycin group *vs* 87% in the levofloxacin group.[17] Additionally, in Venezuela, the *H. pylori* eradication rate associated with clarithromycin triple therapy was 67% *vs* 95% for levofloxacin-based regimens.[18]

Various factors may influence *H. pylori* eradication, with Broutet *et al.* identifying a significant association between age and treatment failure.[19] In another study conducted in Korea that recruited 1,413 patients, female sex and smoking were associated with treatment failure.[20] In the same study, age did not affect eradication rates. In China, age, sex, endoscopic diagnosis and smoking did not show any effect on treatment success rates.[21] An Israeli study showed that the *H. pylori* eradication rate was higher in non-smokers than smokers.[22] In a meta-analysis studying the effect of smoking as a factor associated with treatment failure, the eradication failure rates were significantly higher among smokers than non-smokers.[23] In a study conducted in France that studied the factors associated with eradication failure, smoking was associated with high failure rates.[19] In the same study, peptic ulcer disease was identified as a risk factor for treatment failure. In Greece, age, sex, smoking and ulcer disease showed no effect in terms of *H. pylori* eradication rate.[24] In our study, age, sex, smoking and endoscopic diagnosis did not influence treatment outcomes. The impact of BMI on *H. pylori* eradication is controversial. In a study comparing 40 overweight/obese participants and 41 normal-weight participants, weight showed a negative effect on *H. pylori* eradication rates.[25] However, no difference in the *H. pylori* eradication rate was observed when the eradication rate was studied in various subgroups by BMI.[25] In our study, the *H. pylori* eradication rate was higher in patients with a high BMI.

Conclusions

In conclusion, this study indicates that both clarithromycin and levofloxacin-based regimens are associated with high success rates and can be used in the Kurdistan Region of Iraq for *H. pylori* eradication. *H. pylori* eradication was not associated with age, sex, endoscopic diagnosis and smoking. A high BMI was shown to be associated with high eradication failure rates. Further studies are needed to monitor *H. pylori* antibiotic resistance rates.

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