Clinical research

The efficacy of moxifloxacin-based triple-therapy in first-line treatment of *Helicobacter pylori* infection in Pakistan: randomized controlled trials

Sumaira Khadim[1], Iyad Muhammad Naeem[1], Muhammad Tanveer Alam[2], Hina Rehman[3], Sidra Ghayas[1], Sajjad Haider[1]

[1]Department of Pharmaceutics and Pharmacy Practice, University of Karachi, Karachi, Pakistan
[2]Department of Gastroenterology, Jamal Noor Hospital, Jamal, Pakistan
[3]Department of Pharmacy Practice, Jinnah Sindh Medical University, Karachi, Pakistan

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Corresponding author:
Dr. Sumaira Khadim
Department of Pharmaceutics and Pharmacy Practice
University of Karachi
Karachi, Pakistan
E-mail: sumairakhadim01@gmail.com

Abstract

Introduction: The challenge of eradicating *Helicobacter pylori* through antibiotic treatment is still a significant concern due to the existence of antibiotic resistance. This study aimed to evaluate and compare the efficacy of sequential therapy based on levofloxacin versus triple therapy based on moxifloxacin in treating *H. pylori* infection in patients receiving first-line treatment.
Material and methods: A total of 162 patients who were examined positive for *H. pylori* were randomly assigned to either of 2 groups to receive the following: (a) levofloxacin 500mg BID, amoxicillin 1 g BID, and omeprazole 20 mg BID for the first 5 days, followed by levofloxacin 500 mg BID, tinidazole 500 mg BID, and omeprazole 20 mg BID (LAO-LTO group); or (b) moxifloxacin 400 mg OD, amoxicillin 1 g BID, and omeprazole 20 mg BID (MAO group) for 10 days.
Results: The eradication rate of *H. pylori* in the LAO-LTO group was 58.4% (45/77) and 76.3% (45/59), and in the MAO group it was 81.2% (69/85) and 92% (69/75), respectively, in ITT and PP analyses. Eradication rates of moxifloxacin-based triple therapies were significantly higher than those of levofloxacin-based regimens ($p < 0.001$). The overall incidence of side effects and patient compliance was significantly lower in the moxifloxacin group ($p < 0.005$) than in the levofloxacin group.
Conclusions: Moxifloxacin-based triple therapy could be a significantly more effective first-line eradication treatment as compared to levofloxacin-based sequential therapy for *H. pylori* infection in Pakistan.

Key words: comparison, eradication, *Helicobacter pylori*, levofloxacin.

Introduction

Helicobacter pylori is a microaerophilic pathogen that has a global prevalence of approximately 50% [1]. It is one of the most important factors in the development of peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, chronic gastritis, and gastric cancers [2]. It has been observed that *H. pylori* is accountable for more than 700,000 new cases of cancer globally. The World Health Organization has classified it as a class 1 carcinogen [1]. It is estimated that the prevalence of *H. pylori* infection among adults in Pakistan is around 80–85%. However,

there is a dearth of research on this topic in the Pakistani population [3].

The primary concern in the realm of Helicobacter pylori infection is presently the escalation of resistance to crucial antibiotics in numerous regions across the globe, which fails therapeutic regimens [4]. The results of a 10-year trend analysis indicate a notable rise in the prevalence of resistance to clarithromycin (from 21% to 30%), ciprofloxacin (from 3% to 16%), and tetracycline (from 5% to 20%) in South Asian countries between 2003 and 2022 [5]. However, the attainment of an optimal treatment regimen has been impeded by issues such as antibiotic resistance, toxicity, and challenges with patient adherence. Thus, there is a requirement for effective and well-tolerated novel alternatives in the initial therapeutic approach [6].

Moxifloxacin, a second-generation fluoroquinolone, is a commonly employed therapeutic agent for the management of respiratory and cutaneous infections. Following oral administration, this substance is rapidly absorbed and exhibits good tissue penetration. The medication's pharmacokinetic property of having a half-life ranging from 9 to 16 h allows for the convenience of administering it once per day [7]. Several studies have indicated that triple-therapy regimens containing moxifloxacin are highly effective as a first-line treatment for the eradication of *H. pylori* [7].

This study aimed to compare the efficacy, compliance, and adverse effects of sequential therapy based on levofloxacin versus triple therapy based on moxifloxacin for *H. pylori* eradication in Pakistan, through which improved therapeutic options can be made available for clinical practice.

Material and methods

Patient selection

The present study is an open-label, single-centre, prospective, randomized clinical trial that was executed at the Gastroenterology Department of Jamal Noor Hospital in Karachi, Pakistan. From June 2020 to June 2022, consecutive adult patients were recruited, who were diagnosed with *H. pylori* Infection after performing upper gastrointestinal system endoscopy or by the detection of bacteria in a stool antigen test by using a Rapid Strip HpSA Kit. Most of the patients hailed from rural regions. The criteria for exclusion were as follows: (1) individuals under 18 years of age; (2) the existence of associated conditions that are clinically significant (coagulation disorders, insulin-dependent diabetes mellitus, neoplastic diseases, neurologic, metabolic, haematological or endocrine hepatic, renal, or cardiorespiratory diseases), and gastrointestinal bleeding; (3) pregnancy or breastfeeding; (4) allergy to any of the drugs used in the study; and (5) previous gastric surgery [8].

Ethics

The University of Karachi Institutional Review Board endorsed the study protocol, vide letter No. IBC No. IBC KU-76/19. It was registered as a randomized, standard clinical trial. (ClinicalTrials.gov. identifier: NCT05863858). Each participant in the study submitted written informed consent before enrolment. Good Clinical Practice standards and the Declaration of Helsinki were implemented [9, 10].

Randomization and treatment

At the pre-study visit, an extensive health history and physical examination were conducted. After conducting the baseline assessment, patients who satisfied the eligibility criteria were assigned randomly to either the MAO group or the LAO-LTO treatment group through a lottery-based approach. By the lottery procedure, small, identical paper slips were folded and mixed in a basket. Subsequently, a blindfolded selection was conducted to obtain the slips that were required for this investigation. All selected cases were invited to select a slip from a total pool of assorted slips (half of the slips contained the letter "M" and other half of the slips contained the letter "L"). Patients who selected a slip marked with the letter "M" were assigned to the MAO group, while those who selected a slip marked with the letter "L" were assigned to the LAO-LTO group. The arrangement of the basket was altered. The aforementioned procedure was iterated until the desired sample size was attained [11].

Patients received either of the following 2 regimens for 10 days.

– LAO-LTO group (n = 77): levofloxacin 500 mg b.i.d., amoxicillin 1 gm b.i.d., omeprazole 20 mg b.i.d. for the first 5 days followed by levofloxacin 500 mg b.i.d., tinidazole 500 mg b.i.d., and omeprazole 20 mg b.i.d.
– MAO group (n = 85): moxifloxacin 400 mg o.d., amoxicillin 1 gm b.i.d., omeprazole 20 mg b.i.d.

Sample size

Sample size calculation was performed using the Openepi WHO online calculator. With the help of eradication rates in both groups of 91.3% and 71.6%, confidence levels of 95%, significance level of 5%, and test power of 80%, the calculated minimum sample size was 124 (62 in each group) [12]. Thus, more than 75 patients were recruited in each group to obtain more accurate results.

Study design

The recruited participants were instructed to fill out a questionnaire that included questions about their demographic information, smoking behaviour, familial history of *H. pylori*, any co-existing medical conditions, symptoms before treat-

ment, and endoscopic diagnosis. Patients were apprised of the most frequent adverse effects of their medication and asked to document any side effects they experienced during treatment. If a patient complained about a side effect during the baseline visit, that side effect was not considered to have occurred. In terms of severity, adverse events were ranked as follows: absent, mild (not disturbing the daily routine), moderate (interfering with daily routine), and severe (prohibited regular normal routine) [13, 14]. Upon completion of the treatment regimen, all patients underwent an interview to assess their compliance with medication and to monitor any potential adverse effects. Noncompliance was defined as patients who were reluctant to take the drugs for any reason, an allergic reaction, and feeling ill. Over 80% of medication consumption was used to define therapy compliance, which was determined by a questionnaire and the return of unused drug packets [12].

The assessment of the eradication rate was conducted through stool antigen testing during the fourth to sixth week after treatment. The microbiology laboratory at the hospital conducted stool antigen testing using a Rapid Strip HpSA Kit that used an enzyme immunoassay technique using a monoclonal antibody [15].

Statistical analysis

Rates of *H. pylori* eradication and the occurrence of treatment-related adverse events were selected as the study's primary and secondary outcomes, respectively. Intention-to-treat (ITT) and per-protocol (PP) analyses were used to evaluate the eradication rates. The ITT analysis method was utilized to compare the treatment groups, encompassing all patients as initially assigned. On the other hand, the PP analysis method was employed to compare the treatment groups, involving solely those patients who completed the treatment as initially assigned. 95% CI was calculated for both the ITT and PP analysis. The statistical methods of the χ^2 test and Fisher's exact test were used to evaluate the correlation between demographic and clinical variables and the respective treatment groups. Moreover, adverse events and compliance were also assessed in both groups. The eradication rates of *H. pylori* were also assessed in the groups receiving moxifloxacin and levofloxacin. The IBM-SPSS 26.0 statistical package was used for all analyses. Clinical significance was defined as a *p*-value of 0.05 or lower.

Results

Characteristics of the study groups

The study involved the enrolment of 162 participants infected with *H. pylori* who were randomly assigned to receive either LAO-LTO therapy (n = 77) or MAO therapy (n = 85). The schematic representation of the progression of patients through the study is depicted in Figure 1. Among the patients who were recruited, 134 (83%) completed their allocated regimen. Twenty-eight (17%) patients were excluded from the study. Among the excluded patients, 8 (LAO-LTO group: 8 patients; MAO group; 0patients) were due to poor compliance, 10 (LAO-LTO group: 3 patients; MAO group; 7 patients) due to follow-up loss, 5 (LAO-LTO group: 5 patients; MAO group; 0 patients) discontinued treatment due to adverse events, and 5 (LAO-LTO group: 2 patients; MAO group; 3 patients) did not receive treatment. The final per-protocol analysis comprised 59 patients with LAO-LTO and 75 patients with MAO.

Table I displays the baseline demographic and clinical characteristics of the patients enrolled in both groups. In total, there were 84 male patients and 78 female patients. Upon initial admission, the most commonly reported symptom was abdominal discomfort, accounting for 63.5% (103/162) of cases, followed by dyspepsia (90/162, 55.5%) and then gastroesophageal reflux (78/162, 48.1%). Following the endoscopic assessment, the most frequent endoscopic observation was gastritis, which was identified in 70.3% (114/162) of cases, and its proportion was significantly higher than other findings ($p < 0.001$). Table I also shows that the proportion of low socioeconomic status, married, diabetic, and dyspeptic patients was significantly higher than their counterparts in both treatment groups ($p < 0.05$), while age, gender, body mass index (BMI), smoking, and family history were found to be statistically insignificant in both groups.

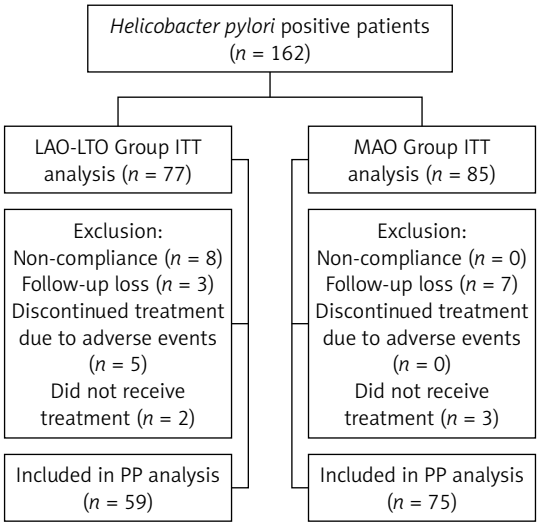

Figure 1. Patient disposition

LAO-LTO – levofloxacin, amoxicillin, omeprazole–levofloxacin, tinidazole, omeprazole, MAO – moxifloxacin, amoxicillin, omeprazole, ITT – intention-to-treat, PP – per protocol.

Table I. Demographic and clinical data

Parameters		Moxifloxacin (n = 85)	Levofloxacin (n = 77)	P-values
Age [years]	< 30	21 (24.7)	22 (28.6)	0.957[ᵀ]
	30–39	27 (31.8)	20 (26)	
	40–49	37 (43.5)	26 (33.8)	
	≥ 50	0 (0)	9 (11.7)	
Gender	Male	50 (58.8)	34 (44.2)	0.640[$]
	Female	35 (41.2)	43 (55.8)	
BMI [kg/m^2]	< 18.5	2 (2.4)	6 (7.8)	0.427[ᵀ]
	18.5–24.9	32 (37.6)	25 (32.5)	
	25–29.9	46 (54.1)	36 (46.8)	
	≥ 30	5 (5.9)	10 (13)	
Socioeconomic status	> 51 K	13 (15.3)	12 (15.6)	0.005[ᵀ*]
	25–50 K	21 (24.7)	27 (35.1)	
	< 25 K	51 (60.0)	38 (49.4)	
Marital status	Married	64 (75.3)	53 (68.8)	0.001[$*]
	Unmarried	21 (24.7)	24 (31.2)	
Smoking	Current smoker	14 (16.5)	15 (19.5)	0.066[ᵀ]
	Never smoked	71 (83.5)	62 (80.5)	
Family history of *H. pylori*	Yes	12 (14.1)	11 (14.3)	0.363[ᵀ]
Co-morbidities	Diabetes	49 (57.6)	45 (58.4)	< 0.001[ᵀ*]
	Hypertension	20 (23.5)	19 (24.7)	
	Others	16 (18.8)	13 (16.9)	
Endoscopic diagnosis	Gastritis	65 (76.4)	49 (63.6)	< 0.001[ᵀ*]
	Gastric/duodenal ulcer	15 (17.6)	21 (27.2)	
	Reflux oesophagitis	5 (5.8)	7 (9)	
Pre-treatment symptoms	Dyspepsia	51 (60)	39 (50.6)	0.045[$*]
	Abdominal pain	63 (74.1)	40 (51.9)	0.205[$]
	Gastroesophageal reflux	38 (44.7)	40 (51.9)	0.217[$]
	Premature fullness	43 (50.6)	30 (39)	0.707[$]
	Weight loss	6 (7.1)	9 (11.7)	0.472[ᵀ]
	Loss of appetite	21 (24.7)	20 (26)	0.131[ᵀ]
Dropout	Follow-up loss	7/10 (70)	3/18 (16.7)	0.067[ᵀ]
	Did not receive treatment	3/10 (30)	2/18 (11.1)	
	Noncompliance	0 (0)	8/18 (44.4)	
	Discontinued treatment	0 (0)	5/18 (27.8)	

[$]*P-value* χ^2 *test,* [ᵀ]*p-value Fisher exact test, *significant p-value at 5%.*

Adverse events and treatment compliance

Table II depicts adverse events and compliance in both groups. The study revealed a statistically significant difference in patient adherence between the moxifloxacin and levofloxacin groups, with the former having a higher level of compliance (p = 0.111). Regardless of the treatment group, the most common adverse effects were diarrhoea (14/162, 8.64%) and vomiting (10/162, 6%). The levofloxacin group exhibited a statistically significant increase in both the frequency and severity of adverse events in comparison to the moxifloxacin group (p < 0.001). Within the moxifloxacin group, most adverse events exhibited mild-to-moderate intensity (12/85, 14%), and none of them was deemed severe enough to necessitate discontinuation of treatment, while 5 patients discontinued treat-

Table II. Adverse events and patient compliance, *n* (%)

Parameters		Moxifloxacin (*n* = 85)	Levofloxacin (*n* = 77)	*P*-values
Adverse events, *n* (%)	Metallic taste	2 (2.3)	3 (3.8)	> 0.999
	Nausea	3 (3.5)	5 (6.4)	> 0.999
	Vomiting	2 (2.3)	8 (10.3)	> 0.999
	Diarrhoea	3 (3.5)	11 (14.2)	> 0.999
	Headache	1 (1.1)	2 (2.5)	> 0.999
	Skin rash	1 (1.1)	2 (2.5)	> 0.999
	Total	12 (14.1)	31 (40.2)	< 0.001[T*]
Severity of adverse events, *n* (%)	Mild	9 (10.5)	17 (22)	< 0.001[T*]
	Moderate	3 (3.5)	9 (11.6)	
	Severe	0 (0)	5 (6.4)	
Patient compliance		75 (88.2)	51 (66.2)	0.111[T]

*[T]P-value fisher exact test, *significant p-value at 5%.*

Table III. *Helicobacter pylori* eradication rates

Eradication rate	Moxifloxacin	Levofloxacin	*P*-values
Intention-to-treat 95% CI	81.2% (69/85) (0.7289–0.8950)	58.4% (45/77) (0.4792–0.6887)	< 0.001[T*]
Per-protocol 95% CI	92% (69/75) (0.8623–0.9776)	76.3% (45/59) (0.6725–0.8534)	< 0.001[T*]

*[T]P-value Fisher exact test, *significant p-value at 5%.*

ment due to severe adverse events in the levofloxacin group.

Eradication of *H. pylori*

Table III presents the rates of eradication of *H. pylori* infection based on the intention-to-treat (ITT) and per-protocol (PP) analyses. The overall ITT eradication rate was 70.3% (114/162). The study results indicate that the moxifloxacin group accomplished a final ITT eradication rate of 81.2% (69/85; 95% CI: 72.9–89.5%), while the levofloxacin group attained a last eradication rate of 58.4% (45/77; 95% CI: 47.9–68.8%). The entire rate of PP eradication was 85% (114/134). The final PP eradication rates were 92% (69/75; 95% CI: 86.2–97.7%) in the moxifloxacin group and 76.3% (45/59; 95% CI: 67.2–85.3%) in the levofloxacin group. In both the ITT and PP analyses, the Fisher exact test indicated a statistically significant difference in eradication rates between the moxifloxacin group and the levofloxacin group ($p < 0.001$).

Discussion

The complete eradication of *H. pylori* remains a significant challenge for medical practitioners because no existing therapeutic regimens have proven the ability to effectively cure the infection in all treated patients. The South Asian region has been associated with a significant increase in antibiotic resistance in *H. pylori*, with rates as high as 98% [16]. According to a recent meta-analysis, Pakistan exhibited the highest prevalence of resistance to amoxicillin, clarithromycin, and tetracycline. Conversely, the highest resistance rates to ciprofloxacin and levofloxacin were observed in India [5]. According to the Maastricht/Florence consensus report published in 2022, the preferred therapeutic approach for *H. pylori* infection in areas with either low or high levels of clarithromycin resistance is bismuth quadruple therapy [17]. However, the effectiveness of this traditional triple regimen has decreased in recent years due to the widespread and expanding usage of antibiotics [18]. Alongside resistance, adverse events and a complex dosing regimen are significant factors contributing to treatment failure because they lead to decreased patient compliance [19].

Several studies were conducted to evaluate the most effective therapeutic regimens to improve the eradication rate and address these issues [8, 15, 19]. This study is an additional endeavour in this regard. In the context of Pakistani patients, the result of this prospective research suggests that both ITT and PP eradication rates were comparatively high with the moxifloxacin-containing regimen as opposed to the levofloxacin sequential regimen (81.2% vs. 58.4% and 92% vs. 76.3%, respectively). This finding is consistent with the results documented in academic literature. Ahmed *et al.* conducted a comparative study between triple-therapy regimens utilizing moxifloxacin and clarithromycin. The study findings suggest that the rates of eradication were relatively high in the

moxifloxacin-based therapy [20]. Similarly, Akpinar *et al.* reported that moxifloxacin-based triple therapy was superior to bismuth-based quadruple therapy for the first-line treatment of *Helicobacter pylori* infection [15]. In the same way, Hassan *et al.* conducted a comparative analysis of the efficacy of nitazoxanide-moxifloxacin-based quadruple therapy and nitazoxanide-levofloxacin-based quadruple therapy in eradicating *H. pylori* infection. The results indicated that the moxifloxacin regimen achieved a higher eradication rate (74%) compared to the levofloxacin-based therapy (64%) [21].

The aforementioned studies indicate that moxifloxacin therapy exhibits greater efficacy compared to levofloxacin-, clarithromycin-, or bismuth-based quadruple therapy. However, several studies have demonstrated that a levofloxacin regimen also yields superior outcomes when compared to a clarithromycin- or bismuth-based quadruple regimen. A recent meta-analysis revealed that levofloxacin triple therapy is more effective at eradicating *H. pylori* infection than clarithromycin-based triple therapy. This may be due to an increase in clarithromycin resistance among these bacteria [22]. Similarly, Alhalabi *et al.* conducted a comparative analysis of the efficacy of bismuth-based and levofloxacin-based regimens in eliminating *H. pylori* infection. Their findings suggest that the levofloxacin-based regimen exhibits a slightly superior eradication rate compared to the bismuth-based regimen (76.92% and 82.05%, respectively) [23]. It would appear that adjustments to treatment recommendations in every country should take into account the unique strains present in that area [24, 25].

The present investigation revealed that the most common adverse events associated with a moxifloxacin-based therapeutic regimen were diarrhoea and nausea (3.5%), with subsequent occurrences of vomiting and metallic taste (2.3%). Conversely, in the levofloxacin group, diarrhoea (14.2%) and vomiting (10.3%) were the most frequently reported adverse events. However, according to Hwang *et al.*, the most frequent adverse events observed in the 14-day moxifloxacin treatment were dyspepsia/bloating (4 out of 78 patients, accounting for 5.1%) and distortion of taste (3 out of 78 patients, accounting for 3.8%) [12]. The total adverse event rate for the moxifloxacin-based regimen was 14.1% (12/85), which was significantly lower than that of levofloxacin therapy 40% (31/77). The findings of this investigation indicate that the incidence and intensity of adverse events are significantly elevated in the levofloxacin group in comparison to the moxifloxacin group ($p < 0.001$). Mild to moderate adverse events were reported in patients treated with moxifloxacin. No adverse effects were significant enough to warrant cessation of medication or impede daily functioning. On the other hand, in the levofloxacin group, 6.4% (5/77) of patients discontinue treatment due to diarrhoea. Compliance rates with a moxifloxacin regimen are greater (88.2%) than those with levofloxacin treatment (66.2%), possibly because of the simpler regimen and fewer side effects. These findings exhibit a notable resemblance to several antecedent investigations [8, 12, 26].

The research is constrained by its trial design, which is limited to a single centre, and the absence of any evaluation of antibiotic resistance in connection with treatment protocols and elimination rates. However, the clinical validity of this research is not compromised by the lack of an antibiotic susceptibility test because it is not conducted routinely in gastroenterological units. Also, the inclusion of a large number of subjects in the study offers hurdles in terms of the feasibility and cost-effectiveness of conducting susceptibility testing on all patients.

In conclusion, the findings of this study indicate that the use of moxifloxacin triple therapy is a highly efficacious and well-tolerated approach for the initial eradication of *H. pylori* infection when compared to the use of levofloxacin-based sequential therapy. Moxifloxacin triple therapy may be a viable recommendation for clinical practices in Pakistan, given its significant rate of eradication, excellent compliance, and safety.

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Conflict of interest

The authors declare no conflict of interest.

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