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ORIGINAL ARTICLE

Pilot study: Comparing efficacy of 14-day triple therapy Clarithromycin versus levofloxacin on eradication of *Helicobacter Pylori* infection in Syrian population single-center experience

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ABSTRACT

Context: Goals: To compare the efficacy of standard triple therapy with clarithromycin versus triple therapy with levofloxacin for treatment of *Helicobacter pylori*-positive infection in a referral hospital in Damascus, Syria. **Design:** pilot prospective open-label randomized controlled trial. **Subjects and Methods:** Eighty treatment-naive patients who tested positive for *H. pylori* gastric infection were randomly assigned to one of two treatment groups with randomization ratio of 50/50. Group (A) was treated with clarithromycin (500 mg), amoxicillin (1000 mg), and esomeprazole (20 mg), each twice/day for 14 days, while Group (B) was treated with levofloxacin (500 mg), amoxicillin (1000 mg), and esomeprazole (20 mg), each twice/day for 14 days.[1] After 6 weeks of treatment, all patients underwent endoscopy and biopsy to evaluate *H. pylori* infection eradication. **Results:** Forty patients were allocated in each group; 37 patients completed the follow-up in each group. Thirteen patients in Group (A) were cured, with an eradication rate of 35.1% according to per-protocol analysis (PPA) and 32.5% according to intention-to-treat analysis (ITT), while in Group (B), 11 patients were cured, with an eradication rate of 29.7% according to PPA and 27.5% according to ITT with $P = 0.80$. No serious adverse events reported in both the groups. **Conclusions:** Clarithromycin is slightly better than levofloxacin in treatment of *H. pylori* gastric infection, but both regimens show low effectiveness with suboptimal eradication rates in our selected population.

Key words: Clarithromycin resistance, Clarithromycin, *Helicobacter pylori,* levofloxacin resistance, levofloxacin, Syria, triple therapy

INTRODUCTION

Syria is expected to have high prevalence of *Helicobacter pylori* infection.[2] *H. pylori* is Gram-negative spiral-shaped bacteria.[3-5] Chronic infection causes diseases such as chronic gastritis, duodenal and peptic ulcers,[3] gastric cancer, and primary gastric mucosa-associated lymphoid tissue (MALT) lymphoma,[5-7] which can be cured by eradication of *H. pylori*.[6,8] The most used protocols in Syria are triple therapy using clarithromycin or levofloxacin with proton pump inhibitor and amoxicillin. There are known resistant types of *H. pylori* against those drugs around the world,[9-15] and there is no standard method for testing the susceptibility of *H. pylori* to antibiotics. Therefore, due to limited data about the efficacy of those protocols in the Syrian patients, we conduct this trial to evaluate the efficacy of those drugs and report our eradication rate.

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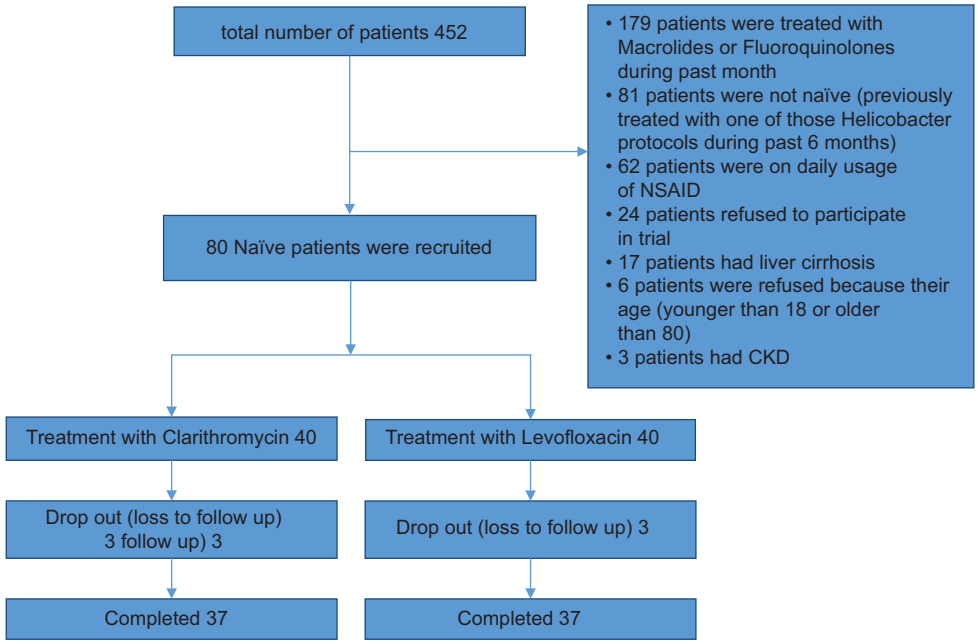

Figure 1: Flow of the study

Table 1: Baseline characteristics of patients

	Clarithromycin (%)	Levofloxacin (%)	*P*
Gender			
Male	15 (37.5)	14 (35)	1.00
Female	25 (62.5)	26 (65)	
Age (mean years±SD)	38.58±14.96	37.20±11.13	0.642
Smoking	6 (15)	5 (12.5)	1.00
Alcoholic	0	1 (2.5)	1.00
Drug side effects			
Anorexia	14 (35)	14 (35)	1.00
Nausea	16 (40)	16 (40)	1.00
Vomiting	4 (10)	1 (2.5)	0.359
Headache	12 (30)	5 (12.5)	0.056
Rash	1 (2.5)	6 (15)	0.048
Unpleasant taste	28 (60)	20 (50)	0.06

SD: Standard deviation

SUBJECTS AND METHODS

The study was carried out from December 2015 to January 2017 in a referral hospital in Damascus, Syria. Study protocol was approved by the ethics committee of the hospital, and it was registered as standard randomized clinical trial (Clinicaltrial.gov, identifier-NCT02541786).

Treatment-naive participants were selected from patients who presented to the gastroenterology clinic undergoing gastroscopy for upper gastrointestinal symptoms and had infection of gastric *H. pylori* confirmed by histology.[16] A written consent was obtained from all participants. The indication of treatment was based on American College of Gastroenterology Guideline on the management of *H. pylori* infection[17] including peptic ulcer, chronic gastritis, primary gastric MALT lymphoma, and intestinal metaplasia.

Authors randomized participants using a computer program. Exclusion criteria of the study were age below 18 and more than 80, history of renal and liver diseases, allergic reaction to the treatment, history of constant NSAID use, pregnancy, and use of antibiotics for 4 weeks before the study. Group (A) was treated with clarithromycin (500 mg), amoxicillin (1000 mg), and esomeprazole (20 mg), each at every 12 h for 14 days,[1] while Group (B) was treated with levofloxacin (500 mg), amoxicillin (1000 mg), esomeprazole (20 mg), each at every 12 h for 14 days.[1] After finishing the treatment period, participants were invited to the clinic for checking drugs side effects. To confirm patient compliance, we asked the patients to bring their remaining medication and counted the rest of their pills. Participants who took at least 90% of their administered drugs were considered as good compliance. Side effects such as headache, nausea, and vomiting were detected by self-report of patients. All participants underwent upper endoscopy after 6 weeks of treatment completion. During endoscopy, five biopsies were retrieved as follows: two from the antrum, one from the incisura, and two from gastric body.[18] All biopsy samples were stained with hematoxylin and eosin and Giemsa[19] in the pathology department. The pathologists were blinded to the treatment arm, and all results were confirmed by two pathologists. Data entry were conducted by a trained doctor, and variables included participants' demographics, smoking history, medications history, findings of physical examinations, endoscopy, and results of biopsy after the treatment completion in a questionnaire. Numerical data were shown as mean and qualitative data expressed as a ratio. Statistical tools such as the Chi-square test and *t*-test were used at appropriate places,

and statistical significance was calculated with a two-tailed test. A $P < 0.05$ was considered as statistically significant. All statistical analyses were done by the R[20] statistics software.

RESULTS

A total of 452 patients were found to have *H. pylori* gastric infection which was confirmed by biopsy. Eighty treatment-naive patients were enrolled in this study (40 patients for each group) and three patients from each group were lost to follow-up; [Figure 1 and Table 1] summarizes the baseline characteristics of the patients. The gender, mean age,and Drug side effects were similar between treatment groups, except Rash, which occurred more frequently in the Levofloxacin group 13 patients in Group (A) were cured, with an eradication rate of 35.1% according to per-protocol analysis (PPA) and 32.5% according to intention-to-treat analysis (ITT), while in Group (B), 11 patients were cured, with an eradication rate of 29.7% PPA and 27.5% ITT with $P = 0.80$.

Odds ratio[21,22] with 95% confidence interval according to ITT was 0.788 [0.302,2.005]., while the odds ratio with 95% confidence interval according to PPA was 0.781 [0.294,2.037].

DISCUSSION

Our study shows that the resistance rate is high in both treatment protocols. Globally, the rate of *H. pylori* clarithromycin resistance ranges from 5.46% to 30.8%,[23] and the occurrence of resistance is increasing worldwide with the highest rate in Asian countries. In early 2017, the World Health Organization listed *H. pylori* as clarithromycin-resistant bacteria.[15,24] The rate of levofloxacin resistance was 25.28% and it was higher in Asia compared to Europe (15%). The incidence of amoxicillin resistance in *H. pylori* seems to increase in South America (97.5%) and Asia,[23,25] which can be explained by macrolides in treating upper respiratory infections and fluoroquinolones in treating urinary tract infections. There are many factors that may explain the resistance in treatment of *H. pylori*-like mechanisms of resistance developed by *H. pylori* to antibiotic used in the treatment of infection, such as the presence or absence of cagA gene.[26] Gender women are developing resistance to clarithromycin, while males are developing resistance to levofloxacin,[13] and finally, with regard to the patients' age, the resistance is more common for clarithromycin in children or young adults than it is in older members.[9]

The previous results are unexpected for us, especially for levofloxacin which prompts us to seek effective ways to treat our patients.

Our study has a number of limitations. The sample size, despite the small size of our sample, was the largest size that can be used with pilot studies.[27] Drugs used in this study are locally manufactured, i.e., clarithromycin (KLACID), levofloxacin (FLOXALIVE), amoxicillin (maxicilline), and esomeprazole (esostom). We cannot confirm that the drug resistance was a cause of our results, as we did not culture of an endoscopic biopsy samples because culturing the *H. pylori* organism is difficult and we do not have this technique. Adherence to medication was from the patient's history. We cannot confirm that all patients were naive to macrolides or fluoroquinolones because there are no detailed medical records for patients in Syria, neither in hospitals nor in the clinic settings. The only method to investigate past medication was to interrogate patients, which was useful if the antibiotics were used for last 2–3 weeks before enrolment. Furthermore, in Syria as in other developing countries, there is a significant misuse of antibiotics, and all antibiotics are easy to get from local pharmacies even without doctor's prescription.[28]

CONCLUSIONS

Treatment regimens using locally produced clarithromycin or levofloxacin were equally ineffective in the treatment of *H. pylori* infections, which may reveal the existence of resistance to the former two drugs. Using therapeutic regimens that do not contain clarithromycin or levofloxacin is a rational option.

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Conflicts of interest

There are no conflicts of interest.

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