Original Article

The Efficacy of Levofloxacin-based Triple Therapy for *Helicobacter Pylori* Eradication after Failure with Clarithromycin-Containing Regimens

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ABSTRACT

Background:
Clinical trials and meta-analyses have reported about 20% failure rates in first-line *Helicobacter pylori* (*H. pylori*) eradication. This reflects the need for effective second-line eradication regimens.

Materials and Methods:
61 patients with *H. pylori* infection who had failed previous non-bismuth clarithromycin-containing first line therapies entered the study. They were given a 14-day levofloxacin-containing triple regimen consisted of pantoprazole 40 mg, amoxicillin 1gr, and levofloxacin 500mg, each given twice daily. Eight weeks after the treatment, *H. pylori* eradication was assessed by 14C-urea breath test.

Results:
All patients completed the study. The eradication rate was 91.8% (95% confidence interval = 84.9% – 98.6%) by both intention to treat and per-protocol analyses. Side effects of therapy were reported by eight patients (13.1%), but they were severe in only two patients (3.2%).

Conclusion:
According to the high *H. pylori* eradication rate and the very low rate of severe adverse effects, levofloxacin-containing triple therapy seems to be a suitable second-line option in case of previous failure by clarithromycin-containing therapies. We suggest further studies with shorter duration of treatment or lower dose of levofloxacin.

Keywords: *Helicobacter pylori*, Eradication, Levofloxacin, Second-line, Clarithromycin

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is an important issue in global health, because almost half of the world's population is infected by the organism. Also, the infection is associated with peptic ulcer disease, gastric adenocarcinoma, and lymphoma (1).

Although many studies have been performed in the era of *H. pylori* treatment during the previous 30 years, the ideal regimen for *H. pylori* eradication has not been identified in some countries (2-4).

Some clinical trials and meta-analyses have reported at least 20% failure rates in *H. pylori* eradication (5-7). This

reflects the need for effective second-line eradication regimens.

According to Maastricht V consensus report, levofloxacin-containing therapies can be used as second-line *H. pylori* treatment in countries with either more or less than 15% clarithromycin resistance rates (8). Furthermore, in some studies, metronidazole- and clarithromycin-resistant *H. pylori* infection has been successfully treated with levofloxacin-containing triple therapy (9-11).

Up to now, no study has evaluated the efficacy of levofloxacin-based triple therapy as a second-line *H. pylori* eradication regimen in Iran, a country with high antibiotic resistance rates. Therefore, we designed a study to assess the effects of the mentioned regimen on those who had failed previous treatment with clarithromycin-containing regimens in this country.

MATERIALS AND METHODS

61 patients with *H. pylori* infection who had failed previous treatments by any of non-bismuth clarithromycin-containing therapies (including standard triple therapy, sequential, concomitant, or hybrid regimens) entered the study. The failure of previous *H. pylori* treatment had been confirmed by 14C-urea breath test (UBT) (Heliprobe Breath Card and Analyser, Kibion AB, Uppsala, Sweden).

The patients were given a 14-day levofloxacin-containing triple therapy, consisted of pantoprazole 40 mg, amoxicillin 1gr, and levofloxacin 500mg, each given twice daily.

Before treatment, written informed consents were taken from all the patients and the protocol was evaluated and approved by the Ethics Committee of Mazandaran University of Medical Sciences, Iran.

The exclusion criteria were: age less than 18 years, pregnancy, breast feeding, concurrent use of anti-coagulants, history of gastric surgery, the presence of heart, renal or hepatic failure, and history of allergy to any of the prescribed drugs.

After starting the second-line protocol, the patients were advised to take all the medications and call the physician in case of any adverse effect. They were also visited after 2 weeks and were asked about the compliance and side effects. Compliance to treatment was considered to be excellent if the patient took more than 90% of the prescribed drugs, good if the patient took 70-90% of the medications, and poor if he/she took less than 70% of the drugs.

Also, side effects were classified as severe, if they stopped daily activities, moderate if they partially interfered with daily activities, and mild if they had no effect on daily activities.

Eight weeks after the treatment, *H. pylori* eradication was assessed by 14C-UBT (Heliprobe Breath Card and Analyser, Kibion AB, Uppsala, Sweden).

At the end of the study, the data were analyzed using SPSS software for windows (version 16). In order to calculate the intention to treat eradication rate, data of all the patients who entered the study were analyzed. But in order to calculate per-protocol eradication rate, only those patients who completed the whole protocol with more than 90% compliance to treatment were included. During the analyses, P values less than 0.05 were considered as statistically significant.

RESULT

All 61 patients completed the study. 32 patients (52.4%) were male and 29 patients (47.6%) were female. The mean (SD) age of the patients was 48.5 (6.3) years.

The previous first-line *H. pylori* eradication regimen of 36 patients was 10-day concomitant therapy (pantoprazole 40 mg, amoxicillin 1 gr, clarithromycin 500 mg, and metronidazole 500 mg, all given twice daily). Also, 16 patients had previously failed 14-day clarithromycin-containing hybrid therapy, three patients had previously failed 14-day clarithromycin- and metronidazole-containing sequential regimen, and six patients had previously failed 14-day standard triple therapy. Other demographic and endoscopic data are shown in table 1.

Among 61 patients in the second-line protocol, *H. pylori* eradication was successful in 56 patients. Since no patient had discontinued the treatment or was lost to follow-up, the eradication rate was 91.8% (95% confidence interval = 84.9% – 98.6%) by both intention to treat and per-protocol analyses. Also, none of the demographic or primary variables was associated with UBT results in univariate logistic regression.

Side effects of therapy were reported by eight

Table 1: Demographic and endoscopic characteristics of the patients

Variables		Number	Percent
Sex	Male	32	52.4
	Female	29	47.6
First-line regimen	Concomitant	36	59
	Hybrid	16	26.2
	Sequential	3	4.9
	Standard triple	6	9.8
Smoking		0	0
History of gastrointestinal bleeding		0	0
NSAID* usage		1	1.6
First-line endoscopic findings	Duodenal ulcer	25	40.9
	Gastric ulcer	10	16.4
	Duodenal and gastric ulcers	14	22.9
	Intestinal metaplasia + erosive gastropathy	3	4.9
	Erosive gastroduodenopathy	5	8.1
	Erosive gastropathy	4	6.5

*NSAID: Non-steroidal anti-inflammatory drug

Table 2: Frequency and severity of side effects of the treatment protocol

Side effect	Number	Percent	Severity
Anorexia	3	4.9	Mild
Tachycardia	1	1.6	Mild
Bloating	1	1.6	Mild
Nausea	1	1.6	Severe
Sore throat	1	1.6	Moderate
Metallic taste	1	1.6	Severe

patients (13.1%) and the most common was anorexia (4.9%). However, only two patients (3.2%) reported severe adverse effect, including nausea, and metallic taste, but no one stopped treatment due to the adverse reactions (table 2).

DISCUSSION

According to the results of our study, more than 90% of the patients could successfully eradicate *H. pylori* infection after failure by clarithromycin-containing regimens.

No study had previously evaluated the efficacy of levofloxacin-containing triple therapy for second-line *H. pylori* eradication in Iran, a country with high antibiotic resistance rates. On the other hand, few similar studies have been performed in Asia. Two recent studies from Taiwan reported 75.3%, 75.6%, and 92.5% per-protocol eradication rates by 7-, 10- and 14-day second-line levofloxacin-containing triple regimens, respectively (12,13). In both studies, levofloxacin was given as 500 mg twice daily and all patients had failed previous therapy with clarithromycin-containing standard triple therapy. Our study showed almost the same eradication rate by 14-day regimen.

Studies from non-Asian countries have also shown that levofloxacin-based therapy can be a suitable option after failure of clarithromycin-containing therapies. In 2010, Zullo and colleagues reported 79.5% per-protocol eradication rate by 10-day levofloxacin-based triple therapy (14). Also, in another study from Italy, the per-protocol eradication rates by 10-day second-line levofloxacin-containing therapies were 90% and 85% for different doses of levofloxacin

(500 mg daily and 500 mg twice daily, respectively) (15).

Comparing our results with the results of other studies, although Iran is a county with high antibiotic resistance rates, the eradication rate of *H. pylori* in our study is comparable to the results achieved by countries with low antibiotic resistance rates.

In vitro studies have shown that levofloxacin retains its activity against *H. pylori*, even if the organism is resistant to clarithromycin and metronidazole. This has also been confirmed in vivo (9-11), and the results of our study are in concordance with the mentioned point.

On the other hand, some studies have suggested bismuth- and metronidazole-containing quadruple therapy as a suitable option after failure by clarithromycin-based regimens. However, three recent meta-analyses have shown the superiority of levofloxacin-based therapies (16-18). Furthermore, levofloxacin-based triple regimen is simpler than bismuth-based quadruple therapy and the patient has to take less number of drugs.

Another important issue in choosing a suitable *H. pylori* eradication regimen is the rate of side effects during treatment. The ideal regimen should have less than 5% severe side effects. In our study, the rate of severe adverse effects was 3%, but no patient discontinued treatment due to adverse reactions.

Previous studies have shown that levofloxacin is a well tolerated drug with mild to moderate and temporary side effects (17,19,20). In a systematic review, the total rate of adverse effects by levofloxacin was 18% and only 3% of patients reported severe adverse reactions (17). This is almost similar to the result achieved by our study.

Of note, a main limitation of our study is the small number of patients. Since hybrid, concomitant, and sequential therapies are almost effective first-line regimens in our country (21-26) more than 700 patients had been treated to obtain this number of patients for the second-line protocol.

The second limitation of our study was the unavailability of *H. pylori* culture. However, a recent study performed in our geographic area reported 22.4% resistance to clarithromycin, 66.1% resistance to metronidazole, and 5.3% *H. pylori* resistance to levofloxacin (27).

The strong point of our study is that it is the first study evaluating the effects of levofloxacin-based triple therapy as the second-line *H. pylori* eradication regimen in Iran, a country with high antibiotic resistance rates.

In conclusion, according to the high *H. pylori* eradication rate and the very low rate of severe adverse effects, levofloxacin-based triple therapy seems to be a suitable second-line option in case of previous failure by clarithromycin-containing therapies. We suggest further studies with shorter duration of treatment or lower dose of levofloxacin for second-line *H. pylori* eradication in Iran.

CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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