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A comparative study of the effect of 10-day esomeprazole containing levofloxacin versus clarithromycin sequential regimens on the treatment of Iranian patients with *Helicobacter pylori* infection

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Abstract

OBJECTIVE:

Helicobacter Pylori (*H. pylori*) treatment may be different depending on the host and microbial factors in each region. The study was planned to estimate the effect of two 10-day esomeprazole containing clarithromycin and levofloxacin sequential therapies on *H. pylori* treatment.

MATERIALS AND METHODS:

Totally, 186 *H. pylori*-infected patients with gastro-duodenal ulcer who had not yet received treatment for infection, were enrolled. We randomly designated patients to group A ($N = 94$) who treated with esomeprazole 40 mg and amoxicillin 1 g bid during the early half of treatment, and continued the same dose of esomeprazole with levofloxacin 500 mg and tinidazole 500 mg bid during the second half of treatment and Group B ($N = 92$) who treated with the identical treatment excepting clarithromycin 500 mg bid as a substitute of levofloxacin. To assess eradication, C14-urea breath test was implemented 8 weeks afterward treatment.

RESULTS:

Finally, 172 patients completed the trial. We calculated 85.1% (95% confidence interval [CI] = 77.9–92.3) and 83.7% (95% CI = 76.2–91.2) eradication intention-to-treat analysis ($P = 0.302$) and so, 93.0% (95% CI = 87.6–98.4) and 90.0% (95% CI = 83.6–96.3) eradication by per-protocol analysis ($P = 0.420$) for Group A and B, respectively. No significant difference was seen among regimens. Drug adverse reactions were not significantly different between regimens. Group A had a 97.8% adherence rate to treatment and Group B had 98.9%.

CONCLUSIONS:

Both esomeprazole containing sequential regimens including levofloxacin and clarithromycin showed good eradication rates in spite of significant differences in antimicrobial resistance patterns *in vitro*. The efficacy of esomeprazole in lowering gastric acidity beside its antimicrobial effect should be considered in *H. pylori* regimens.

Keywords: Clarithromycin, esomeprazole, *Helicobacter pylori*, levofloxacin, sequential treatment

Introduction

One of the most prevalent infections across the world is *Helicobacter Pylori* (*H. pylori*) which has infected almost half of the world populations with higher prevalence in developing countries (30%–80%) than in developed countries (<10%). It is a Gram-negative bacillus which embeds in the stomach.[1,2,3] The role of *H. pylori* is explained in some gastric disorders such as peptic ulcer disease, chronic gastritis, and even gastric carcinoma. One of the major factors in *H. pylori* treatment failure is primary antimicrobial resistance patterns. In addition to antibiotic resistance several other factors such as patients' adherence to treatment, gastric acidity, CYP2C19 polymorphism, high bacterial count, and pathogenicity of microorganisms may influence the outcome of *H. pylori* treatment.[4] Although several studies have been accomplished to find out the ultimate regimen for eliminating the bacteria, results clearly demonstrate a discrepancy in various geographic regions which is sometimes disappointing. The reasons are abundant, but the main factors include the primary resistance to antibiotics and the wide range of bacterial diversity.[4] High resistance to clarithromycin is considered as a major factor for *H. pylori* treatment failure across the world.[5]

Fluoroquinolones can be chosen as an alternative for first-line therapy when the resistance to clarithromycin reaches further than 20% and at the same time, the resistance to fluoroquinolone is lower than 10%.[6] *H. pylori* resistance rate for different antibiotics were evaluated as follows in Iran: 61.6% to metronidazole, 22.4% to clarithromycin, 16.0% to amoxicillin, 12.2% to tetracycline, 21.0% to ciprofloxacin, 5.3% to levofloxacin, and 21.6% to furazolidone.[7] In this regard, we can choose levofloxacin in its place of clarithromycin in first-line *H. pylori* regimens.

On the other hand, esomeprazole is more effective in gastric acid suppression especially in higher doses compared to other proton pump inhibitors (PPIs). Besides, previous studies revealed that esomeprazole has an anti-*H. pylori in vitro* effect.[8]

This trial was planned to evaluate the effect of two 10-day esomeprazole-containing sequential therapies consisting of clarithromycin and levofloxacin on *H. pylori* treatment.

Materials and Methods

One hundred and eighty-six naïve *H. pylori*- infected adults with endoscopic confirmation of gastroduodenal ulcer or erosion participated in this randomized clinical trial. We performed a rapid urease test and/or histological staining on samples that were taken during endoscopy to confirm the presence of *H. pylori*.

Participants younger than 18, any history of systemic disease including liver, heart, pulmonary, and renal diseases, malignancy, history of gastric surgery, those who received antibiotics and bismuth during four preceding weeks, active alcohol user, anticoagulant or corticosteroid user, pregnancy, lactation, and any history of allergic reactions to the prescribed medications were excluded from the study.

Regarding the previous study, we found a 16% eradication rate difference[9] between the regimens. The sample size was calculated at least 184 patients in this study (92 patients in each group), based on the alpha coefficient = 0.05, beta coefficient = 0.2, and power = 85%.

All the participants were fully informed about the treatment strategies before they signed the consent form. The ethics committee of the Iran University of Medical Sciences (IUMS) confirmed this study by the number of IUMS, 105/5840/93. Moreover, it was entered into the records of the Iranian Registry of Clinical Trials (IRCT2015030820178N2).

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The patients were randomly allocated for the treatment regimens through a random numbers table generated by a computer.

Group A (94 patients) treated with tablet esomeprazole 40 mg half an hour before breakfast and before dinner, and capsule amoxicillin 1000 mg two times/day during the early half of treatment, and continued with tablet esomeprazole 40 mg half an hour before breakfast and before dinner, plus capsule levofloxacin 500 mg (Tavanex, Abidi Pharmaceutical Company) two times/day and tablet tinidazole 500 mg two times/day during the second half of treatment.

Group B (92 patients) treated with tablet esomeprazole 40 mg half an hour before breakfast and before dinner, and capsule amoxicillin 1000 mg two times/day during the early half of treatment, and continued with tablet esomeprazole 40 mg half an hour before breakfast and before dinner, with capsule clarithromycin 500 mg two times/day and tablet tinidazole 500 mg two times/day during the second half of treatment.

Demographic data, smoking, history of nonsteroid anti-inflammatory drugs (NSAIDs) or aspirin usage, sign of bleeding from upper gastrointestinal tract in history (GIB), and the results of endoscopy (size and location of ulcers/erosions, and bulbar deformity) were recorded.

Regular and continuous use of the medications were recommended even the patients had tolerable (mild to moderate) adverse effects. Patients were asked to record drug side effects and medication consumption on a daily basis self-reporting forms. All patients were visited 10 days after beginning the regimens to assess their compliance (pill count) and drug adverse reactions. The severity score of adverse reactions was categorized as 0: no evidence of adverse reactions; 1: mild (no restriction for doing activity in a day); 2: moderate (minor restriction for doing activity in a day); and 3: severe (intense restriction for doing activity in a day). The patients' adherence rates were defined as excellent, good, and poor if the patient had used up more than 90%, 60%–90%, and <60% of prescribed medications, respectively.[10]

All participants underwent a C^{14}-urea breath test (UBT) 8 weeks afterward the treatment completion. They were requested to swallow 37kBq (lCi) enclosed 14 C-marked urea compound (Helicap Institute of Isotopes, Budapest, Hungary) with water. Around 10 min later, they breathed out inside a container (Heliprobe breath card, Kibion Uppsala, Sweden) till the card color altered. Ultimately, Geiger–Muller counter (Heliprobe Analyser, Kibion AB) was used to measure radioactivity. Regarding radioactivity measurements, counts >50 counts per minute (cpm) were considered as positive UBT and count <25 cpm were reflected as negative UBT. Moreover, borderline results were considered eradicated. Details of the study protocol are shown in Figure 1.

Open in a separate window

Figure 1

Flowchart of study protocol

Analysis of statistics

Data were analyzed through SPSS for Windows v19.0; SPSS Inc., Chicago, IL, USA. Quantitative parameters were reported as mean ± standard deviation analysis of variance test was used to compare means among two groups of study. We used Chi-square and/or Fisher's exact tests to compare proportions between treatment groups and $P < 0.05$ means statistically significant differences.

All patients who participated in the study were considered for the intention to treat (ITT) analysis. The patients who completed the study totally and/or had at least 80% adherence to treatment, were considered for preprotocol (PP) analysis. Data were blindly analyzed by a statistician.

Results

One hundred and seventy-two participants with the mean age of 42.28 (± 0.29) years (range; 18–81) completed the study (86 patients in each group). The majority of our patients 52.68% (98/186) were male. No significant differences were found between treatment groups regarding demographic information, history of GIB, taking NSAIDs, smoking, and endoscopic characteristics [Table 1].

Table 1

Demographic, clinical characteristics, and endoscopic findings of the patients

	Group A (94)	Group B (92)	*P*
Male/female (*n*)	46/48	42/50	NS
Age (mean±SD; years)	44.05±13.66	42.49±14.17	NS
Smokers, *n* (%)	15 (16.3)	12 (13.0)	NS
History of GIB, *n* (%)	15 (16.1)	22 (23.9)	NS
History of NSAID consumption, *n* (%)	18 (19.1)	17 (18.5)	NS
EGD, *n* (%)			
Duodenal ulcer	48 (51.1)	38 (41.3)	NS
Ulcer size (>10 mm)	10 (10.6)	8 (8.6)	
Bulbar deformity (mild-moderate)	4 (4.2)	3 (3.2)	
Gastric/duodenal erosion	24 (25.5)	31 (33.7)	NS
Gastric ulcer	21 (22.3)	23 (25.0)	NS
Ulcer size (>10 mm)	8 (8.5)	9 (9.7)	

NS=Nonsignificant statistically, *n*=Number, SD=Standard deviation, EGD=Esophagogastroduodenoscopy, GIB=Gastrointestinal bleeding, NSAIDS=Nonsteroid anti-inflammatory drug

Fourteen patients (7.5%) did not complete the study: Seven patients lost follow-up visits and UBT test, 3 had poor compliances, and 4 patients interrupted medications [Figure 1].

We calculated 85.1% (95% confidence interval [CI] = 77.9–92.3) eradication in Group A and 83.7% (95% CI = 76.2–91.2) eradication in Group B by intention-to-treat analysis ($P = 0.302$). And so, we calculated 93.0% (95% CI = 87.6–98.4) eradication in Group A and 90.0% (95% CI = 83.6–96.3) eradication in Group B ($P = 0.420$) by per-protocol analysis. No significant difference was found among the regimens regarding the eradication rate analysis [Table 2].

Table 2

Comparison of success rate in treatment *Helicobacter pylori* infection between two groups

	Group A		Group B		95% confidence interval	*P*
	Patients	Eradication rate (%)	Patients	Eradication rate (%)		
ITT analysis	80/94	85.1	77/92	83.7	−9.0-11.83	0.302
PP analysis	80/86	93.0	77/86	90.0	−5.3-11.3	0.420

ITT=Intention to treat, PP=Preprotocol, Group A=Levofloxacin-based regimen, Group B=Clarithromycin-based regimen

The adherence rate was estimated at 97.8% (84/86) for patients in Group A and so 98.9% (85/86) for patients in Group B. The result of this study did not show a significant difference between regimens based on the severity of side effects. The majority of deleterious effects occurred in the second 5 days of the treatment and so were mild and transient. The most prevalent deleterious reactions were nausea and insomnia in Group A and bitter taste in Group B [Table 3].

Table 3

Frequency of drug-related side effects in each group

	Group A (94)	Group B (92)	Total (186)	*P*
Bitter taste (%)	4 (4.25)	16 (17.39)	20 (10.75)	0.01
Dry mouth (%)	1 (1.06)	2 (2.17)	3 (1.61)	NS
Nausea (%)	7 (7.44)	4 (4.34)	11 (5.91)	NS
Diarrhea (%)	4 (4.25)	2 (2.17)	6 (3.22)	NS
Skin rash (%)	0	1 (1.08)	1 (0.53)	NS
Dizziness (%)	3 (3.19)	2 (2.17)	5 (2.68)	NS
Headache (%)	4 (4.25)	2 (2.17)	6 (3.22)	NS
Insomnia (%)	7 (7.44)	0	7 (3.76)	0.001

NS=Nonsignificant statistically

Discussion

Although various regimens have been proposed for *H. pylori* treatment, the ideal treatment has not been determined until now. Currently, the standard clarithromycin triple therapy is at the lowest success rate levels. One of the main factors for treatment failure is rapidly developing resistance to antibiotics across the world. It seems when the resistance rate of clarithromycin reaches more than 15%–20%, the

treatment rate of standard triple therapy drops to <80%.[11] This regimen has a lower success rate in developing countries. It is associated with the diversity of *H. pylori* pathogenicity, resistance pattern to antibiotics, combination and/or dosage of medications, the treatment period, and PPI metabolizer polymorphism.[12] Clarithromycin-based sequential regimen was developed and considered as an effective regimen for first-line therapy. However, the superiority of this regimen was not demonstrated in some studies especially in Asian patients. Dual resistance to clarithromycin and metronidazole was considered as the main cause for these results.[9,13,14]

Based on a systematic review, clarithromycin-based sequential therapy achieved 84.3% (95% CI; 82.1%–86.4%), and 72.8% (95% CI; 61.6%–82.8%) eradication rates in infected patients totally and patients who infected by strains that were resistant to clarithromycin, respectively.[15]

One of the previous studies showed that the combination of clarithromycin, bismuth, PPI, and amoxicillin as a second-line regimen could achieve 88.4% PP eradication rate when the patients had not received clarithromycin in first-line therapy.[16]

Moreover, several studies were designed to assess the effect of clarithromycin-containing sequential therapies by substituting PPI, antimicrobial medications, and changing the duration of treatments.

Levofloxacin is one of the antimicrobial alternatives which has been used in some triple and sequential levofloxacin-based treatments as the first-line regimen with different results.

A single-arm study showed that 72.2% overall eradication rate was achieved by prescribing a 2-week levofloxacin triple therapy including lansoprazole 30 mg bid, levofloxacin 500 mg once a day, and amoxicillin 1 gr bid [17]

Berning *et al*.[18] found that 10-day pantoprazole containing levofloxacin-based sequential therapy could achieve an overall 78.2% eradication rate.

Another study[19] compared two 14-day omeprazole containing levofloxacin- versus clarithromycin-based sequential regimens and they found 87.6% and 76% PP eradication rates, respectively. They found better results by replacing clarithromycin with levofloxacin in sequential regimens.

One of the previous studies compared the effect of sequential therapies. The eradication rates were measured as 80.8% for omeprazole containing clarithromycin-based, 96.0% for levofloxacin-based 250 mg/day, and 96.8% for levofloxacin-based 500 mg/day sequential therapies. They also found better results by replacing clarithromycin with levofloxacin in a sequential regimen. Eradication rates were not significantly different after increasing the dose of levofloxacin in this study.[9]

A meta-analysis[17] showed that, compared to the first-generation of PPIs, esomeprazole, and rabeprazole containing regimens had better *H. pylori* eradication rates. This clinical advantage is more noticeable in regimens containing esomeprazole 40 mg bid. This is due to the CYP2C19 metabolizer effect.

Another study found that esomeprazole containing levofloxacin-based concomitant quadruple regimen during 5 days was more effective, safer, and cost-effective than a 10-day levofloxacin-based sequential regimen.[20] They found 96.5% eradication in the concomitant quadruple therapy and 95.5% eradication in the sequential therapy regarding per-protocol analysis.

It means that a 5-day concomitant quadruple therapy had the same efficacy as a 10-day sequential therapy. Better results were achieved by substitution of esomeprazole as a PPI and consuming all the drugs concomitantly, in this study.

The increasing utilization of quinolones in various regions is likely the cause of the intensified resistance to them which may lower the success rates of salvage therapy.[18] Levofloxacin containing regimens should be considered as salvage therapy when *H. pylori* infection does not respond to the first or second-line therapy.[21]

In addition, the dose and type of suggested PPIs may determine the effectiveness of *H. pylori* treatment across the world.[12] Esomeprazole is more effective in gastric acid suppression, especially in higher doses compared to the other PPI. Furthermore, some studies found the anti-*H. pylori* effect for

esomeprazole at least *in vitro*.[8]

In this study, we found the eradication rates of 93% and 90% in PP analysis and 85.1% and 83.7% in ITT analysis for levofloxacin- and clarithromycin-based regimens combined with esomeprazole as a PPI, respectively. Although the *in vitro* resistance rates of clarithromycin and levofloxacin were reported 22.4% and 5.3%, respectively in Iran,[7] we did not find any statistically significant difference between treatment groups regarding the eradication rates. It seems to be directly related to the high dose of esomeprazole in this regimen. Both regimens were safe and effective.

Esomeprazole containing levofloxacin-based sequential therapy might be an alternative for first-line treatment wherever clarithromycin resistance rate is high by the result of this study and the previous ones.[9,21]

There were some limitations to this study. *H. pylori* culture was inaccessible and expensive so that we had to design the trial based on previous *in vitro* resistance patterns in Iran. It was the main limitation of our study. Nevertheless, *in vitro* antimicrobial-resistance pattern could not always predict *in vivo* nonresponsiveness rates. The second one was the small sample size.

Conclusions

Esomeprazole containing sequential regimens including levofloxacin and/or clarithromycin showed good eradication rates in spite of significant antimicrobial resistance rate differences *in vitro*. Both acid-lowering and anti-microbial effect of esomeprazole should be considered in *H. pylori* treatment regimens. It seems that levofloxacin-based regimen could be put aside for only salvage therapy in Iran.

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Conflicts of interest

There are no conflicts of interest.

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