A comparison between conventional triple therapy and sequential therapy on tolerance of treatment and eradication of *Helicobacter pylori* infection in Egyptian patients Waleed A. Ismail, Ehab F. Mostafa

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Received 24 January 2018 Accepted 26 March 2018

The Egyptian Journal of Internal Medicine 2018, 30:90–95

Context

Antimicrobial resistance has decreased eradication rates for *Helicobacter pylori* (*H. pylori*) infection worldwide. Sequential therapy (ST) has been suggested as an alternative to conventional triple therapy (TT) for the first-line treatment of *H. pylori*. **Aim**

The purpose of this study was to compare the efficacy and tolerance of levofloxacinbased ST with clarithromycin-based TT.

Materials and methods

This is a randomized open-label clinical trial carried out on 134 patients with dyspepsia selected from Outpatient Clinic of Hepatology and Gastroenterology Department, Zagazig University Hospital, from October 2015 till September 2016. All patients were *H. pylori* positive as evidenced by C13-urea breath test and rapid urease test. Patients were divided into two groups: group I 67 patients received levofloxacin-based ST whereas group II 67 patients received clarithromycin-based TT for 14 days. Eradication rates, drug compliance, and adverse events were compared among the two regimens.

Results

The intention-to-treat eradication rates were 71.6% for TT and 91% for ST (P=0.004). The adverse effects including nausea, vomiting, abdominal pain, and diarrhea were less in levofloxacin-based ST than clarithromycin-based TT, but there was no statistically significant difference (all P>0.05).

Conclusion

The efficacy of levofloxacin-based ST is significantly better in the treatment of *H. pylori* than TT, and it also shows good tolerability. Countries like Egypt seem to have a high clarithromycin resistance, and a large-scale clinical trial is needed to choose the first-line therapy for eradication of *H. pylori* infection.

Keywords:

conventional triple therapy, Helicobacter pylori infection, sequential therapy

Egypt J Intern Med 30:90–95 © 2018 The Egyptian Journal of Internal Medicine 1110-7782

Introduction

Helicobacter pylori (H. pylori) is the main cause of the upper gastrointestinal disorders, which include peptic ulcer disease (gastric and duodenal), chronic gastritis, gastric mucosal-associated lymphoid tissue lymphoma, and gastric cancers [1]. In the latest years, it has been suggested the possible role of H. pylori infection with numerous extragastric disorders, which includes neurodegenerative, cardiovascular problems and metabolic, as well as hepatobiliary, pancreatic, and colorectal illnesses. Furthermore, research suggests that this bacterium may be related to the development of skin disorders, which includes urticaria in addition to rheumatic diseases [2]. The most often used strategy is triple therapy (TT). This therapy is composed of a proton pump inhibitor (PPI) (lansoprazole 30 mg/12 h, rabeprazole 20 mg/12 h, omeprazole 20 mg/12 h, esomeprazole 40 mg/24 h, or pantoprazole 40 mg/12 h), amoxicillin (1 g/12 h), and clarithromycin (500 mg/12 h) taken for 7–14 days. The length of therapy is arguable, even though a meta-analysis cautioned that 14 days gives eradication rates 5% higher than the ones for 7 days. In cases of hypersensitivity to penicillin, metronidazole is the one of choice to replace amoxicillin, as it is far equally effective and considered equal [3]. Many areas of the world that have been studied on multiple occasions display growing resistance rates to antibiotics in each high and middle/low income countries. A current assessment on the global emergence of *H. pylori* antibiotic resistance confirms that eradication rates have been declining whereas the prevalence of antibiotic resistance rate was growing.

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Moreover, clarithromycin resistance rates have now reached 30% in Italy and Japan, 40% in Turkey, and 50% in China, although it is 15% in Sweden and Taiwan [4]. A recent study in Mansoura Gastroenterology Surgical Centre, Egypt, included 82 patients experi encing upper gastrointestinal symptoms. Biopsy samples have been taken from patients with endoscope and subjected to microbiological culture for H. pylori. Antibiotics susceptibility was decided for the isolates to clarithromycin, amoxicillin, metronidazole, cipro floxacin, and levofloxacin, and it was found that there was high occurrence of H. pylori strains resistant to clarithromycin (71%), which was thought to be the primary line antibiotic therapy in treatment of H. pylori; however, resistance patterns had been much less closer to levofloxacin (23.2%). The study attracts interest that fluoroquinolone resistance is less than that for first-line therapy, which may be a better substitute for first-line antibiotics [5].

Thus, the aim of this study was to compare the efficacy and tolerance of levofloxacin-based sequential therapy (ST) with TT.

Materials and methods

This is a randomized open-label clinical trial carried out on 134 patients with dyspepsia attending the outpatient clinic of Hepatology and Gastroenterology Department of Zagazig University hospitals from October 2015 to September 2016. They were proved to be H. pylori infected as evidenced by using C13-urea breath test and Campylobacter-like organism (CLO) test. Only patients proved to be *H. pylori* positive in both tests were included in the study. Patients who were less than 18 years old, pregnant or breastfeeding women, patients previously treated with H. pylori eradication therapy, patients who previously underwent gastric surgery, and patients with malignant neoplasm were all excluded. All study patients were subjected to detailed medical history and clinical examination, C13-urea breath test, and upper endoscopy with examination of the esophagus, stomach, and duodenum to the second part using Olympus CV-150 or Pentax EPM-3500. A rapid urease test (CLO test; Kimberly-Clark Ltd., Draper, Utah, USA) was performed for all patients studied. We obtained biopsy specimens from the antrum and from the corpus of the stomach. When the CLO test showed red-violet color within 24 h at room temperature, the diagnosis of H. pylori infection was made. The study patients were randomly divided into two groups using a table of random numbers:

- (1) The first group (67 patients) was randomly assigned to ST in the form of 30-mg proton pump inhibitors (lansoprazole) twice daily and amoxicillin 1g twice daily for the first 5 days followed by 30-mg proton pump inhibitors (lansoprazole) twice daily and levofloxacin 500 mg once daily and tinidazole 500 mg twice daily for the second 5 days.
- (2) The second group (67 patients) was randomly assigned to TT in the form of 30-mg proton pump inhibitors (lansoprazole) twice daily and amoxicillin 1g twice daily and clarithromycin 500 mg twice daily for 14 days.

We interviewed patients to investigate compliance and the adverse effects of the drugs, including abdominal bloating, abdominal pain, bitter taste, constipation, dizziness, epigastric pain, general weakness, halitosis, headache, diarrhea, loss of appetites, nausea, oral ulcer, skin eruption, sleeping tendency, and vomiting. The term 'less than 80% compliance' was described as termination of the therapy before the eighth day owing to adverse drug reaction.

Response to treatment was evaluated 6 weeks after cessation of therapy using C13-urea breath test.

This study protocol was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Institutional Review Board of each participating facility. Informed consent was obtained from all patients.

Statistical analysis

Statistical package for the social sciences (SPSS) for Windows (version 20; SPSS Inc., Chicago, Illinois, USA). All tests used were two-tailed. A P value less than 0.05 was considered as statistically significant. Continuous data were presented as mean±SD. Comparative analysis of continuous data was done using Student's t-test. Categorical data were expresses as number (percentage) and summarized in a contingency table. Comparative analysis of categorical χ^2 or Fisher's exact test when absolute frequency of any cell in contingency table was greater than or equal to 5 or less than or equal to 5, respectively. Univariate and multivariate logistic regression analyses were performed for evaluating independent-associated factors with successful H. pylori eradication.

Results

There was no significant difference between patients who took ST and those who took TT regarding demographic features: age, sex, smoking, and also clinical presentation (all P>0.05; Table 1).

Table 1 Demographic features and clinical presentation of the studied patients (n=134)

Parameters	Sequential (<i>n</i> =67) [<i>n</i> (%)]	Triple (<i>n</i> =67) [<i>n</i> (%)]	P value
Age	35.05±8.41	35.64±10.35	0.715
Sex			
Male	35 (52.2)	31 (46.3)	0.489
Female	32 (47.8)	36 (53.7)	
Smoking			
Yes	21 (31.3)	20 (29.9)	0.851
No	46 (68.7)	47 (70.1)	
Epigastric pain			
Yes	41 (61.2)	44 (65.7)	0.591
No	26 (38.8)	23 (34.3)	
Nausea			
Yes	16 (23.9)	12 (17.9)	0.395
No	51 (76.1)	55 (82.1)	
Vomiting			
Yes	17 (25.4)	26 (38.8)	0.096
No	50 (74.6)	41 (61.2)	
Heart burn			
Yes	21 (31.3)	18 (26.9)	0.568
No	46 (68.7)	49 (73.1)	
Hematemesis			
Yes	1 (1.5)	2 (3)	1
No	66 (98.5)	65 (97)	

Figure 1

There was no statistically significant difference between the studied groups according to endoscopic features (all P>0.05; Table 2).

Eradication of *H. pylori* was found to be significantly higher in individuals who underwent ST when compared with those who underwent TT (P<0.05; Table 3 and Fig. 1).

There was no statistically significant difference between the studied groups according to termination of therapy because of adverse effects (P>0.05; Table 4).

Regarding the adverse effects associated with *H. pylori* treatment, no statistically significant difference was detected between both studied groups (all P>0.05; Table 5).

There was a significant positive association between ST and TT in *H. pylori* eradication even after adjustment of other confounding variables (both *P*<0.05; Table 6).

Parameters	Sequential (<i>n</i> =67) [<i>n</i> (%)]	Triple (<i>n</i> =67) [<i>n</i> (%)]	P value
Antral gastritis	38 (56.7)	40 (59.7)	0.726
Pangastritis	18 (26.9)	15 (22.4)	0.547
Duodenitis	9 (13.4)	4 (6)	0.242
Hiatus hernia	9 (13.4)	6 (9)	0.411
GERD	29 (43.3)	20 (29.9)	0.106

GERD, gastroesophageal reflux disease.



Response to standard triple and sequential therapy.

Table 3 Response to treatment of Helicobacter pylori by C13urea breath test of the studied patients (n=134) by intentionto-treat analysis

Parameters	Sequential (n=67) [n (%)]	Triple (<i>n</i> =67) [<i>n</i> (%)]	P value
Responders	61 (91)	48 (71.6)	0.004
Nonresponders	6 (9)	19 (28.4)	

Table 4 Termination of the rapy because of adverse effects (n=134)

Parameter	Sequential (<i>n</i> =67) [<i>n</i> (%)]	Triple (<i>n</i> =67) [<i>n</i> (%)]	P value
Termination of therapy	2 (3)	3 (4.5)	1

Table 5 Adverse effects of the treatment of studied groups (n=134)

Parameters	Sequential (N=67) [n (%)]	Standard (<i>N</i> =67) [<i>n</i> (%)]	P value
Nausea			
Yes	2 (3)	3 (4.5)	0.649
No	65 (97)	64 (95.5)	
Vomiting			
Yes	8 (11.9)	8 (11.9)	1
No	59 (88.1)	59 (88.1)	
Abdominal pai	n		
Yes	3 (4.5)	4 (6)	0.698
No	64 (95.5)	63 (94)	
Diarrhea			
Yes	4 (6)	4 (6)	1
No	63 (94)	63 (94)	

 Table 6 Association between type of treatment and eradication of Helicobacter pylori (n=134)

Model	OR	95%CI of OR	P value
Crude			
Sequential	4.02	1.49-10.86	0.006
Standard	RC	RC	RC
Adjusted ^a			
Sequential	4.09	1.48 : 11.32	0.007
Standard	RC	RC	RC

CI, confidence interval; OR, odds ratio. ^aAdjusted for age and sex. The r by c chi-square test which one of the methods to estimate.

Discussion

There are very few data about the prevalence of *H. pylori* infection in Egyptian population. El Dine *et al.* [6] observed that the general seropositivity for anti-*H. pylori* antibodies was 91.7%, and the rate of infection was different in many age groups, with an increasing fashion in older ages.

Low socioeconomic class, low body weight and height, living in rural areas, and decrease academic fame have been threat factors for the acquisition of *H. pylori*, and the highest prevalence was within the healthy asymptomatic populace comprising both adults and the pediatric age group in Egypt [7–9].

This high prevalence rate gives an attention to an important question, "what is the most effective treatment regimen?"

In our study, the male and female percentages were 52.2 and 47.8% in TT group, and 46.3 and 53.7%, in levofloxacin-based ST group, which was not significant, and it is similar to many previous studies ;in which the ratio is insignificant [10–12].

There is no significant difference of *H. pylori* infection between adult men and women [13].

Our study showed that 85 of 134 patients complained of epigastric pain. This was near to the study done by Karthick *et al.* [14] which was conducted on 100 patients with epigastric pain of gastric origin; 83 of them had dyspepsia, and of them, 61 were *H. pylori* positive (73.4%).

Marzio *et al.* [15] concluded that *H. pylori* infection does not seem to be associated with a specific symptom.

Our study showed that gastritis is the most common endoscopic feature. This agrees with Diab *et al.* [16] who found a strong association between *H. pylori* infection and patients with gastritis, with existence of *H. pylori* infection in 63 (82.9%) of 74 patients with gastritis.

Chronic *H. pylori* gastritis affects two-thirds of the world's population [17]. Kyoto global consensus 2015 agrees that the most common cause of chronic gastritis worldwide is infection with *H. pylori* [18].

Our study showed that of 134 patients, 49 patients had gastroesophageal reflux disease (GERD). Corley [19] *et al.* determined that the presence of antibodies against *H. pylori* had a robust inverse association with GERD symptom frequency and severity. This recommends that if the associations are causal, a portion of the threat for GERD may be related to the absence of gastric colonization with the *H. pylori* bacterium [19].

Rubenstein *et al.* [20] were unable to detect a negative association between *H. pylori* and GERD symptoms. Grande *et al.* [21] shows no significant role of *H. pylori* infection in the development of GERD or in the pathogenesis of reflux esophagitis. Our study results showed that comparison between conventional TT and levofloxacin-based ST of *H. pylori* showed that eradication of *H. pylori* was found to be significantly higher in individuals who took ST when compared with those who took TT (91 vs. 71.6%; P < 0.05).

Maysaa *et al.* [5] reported in a study done in Mansoura University hospitals, Egypt, that there is a high prevalence of *H. pylori* resistant strains to clarithromycin (71%), which is thought to be the firstline antibiotic therapy in treatment of *H. pylori*, whereas resistance patterns were less toward levofloxacin (23.2%) [5].

This is similar to Polat *et al.* [22] who found that the 10-day ST achieves drastically higher eradication rate that TT (90% in sequential versus 57% in standard therapy groups), with a statistical significance (P<0.000). They concluded that clarithromycin resistance is the main cause of *H. pylori* eradication failure [22].Qian *et al.* [23] discovered that standard ST produced unacceptably therapeutic efficacy in China. Simplest levofloxacin-containing ST produced a suitable end result [23].

Zullo *et al.* [24] found that levofloxacin-based sequential treatment has been proved to be better than standard TTs, confirming that the 'sequential' administration of drugs is a successful therapeutic strategy for *H. pylori* infection.

Romano *et al.* [25] found that in an area with greater than 15% prevalence of clarithromycin-resistant *H. pylori* strains, levofloxacin-containing ST is more effective than clarithromycin-containing ST, with 96.8 versus 80.8% (*P*<0.0001).

Our study showed that the adverse effects including nausea, vomiting, abdominal pain, and diarrhea are less in levofloxacin ST than standard therapy, but it was of no statistically significant difference (all P>0.05).

This is similar to Polat *et al.* [22] and Qian *et al.* [23] who showed that levofloxacine-based ST is better tolerated than clarithromycine based-TT with better eradication rate.

Conclusion

Efficacy of levofloxacin-based ST is significantly better in treatment of *H. pylori* than TT, and it also shows good tolerability. Countries like Egypt seem to have a high clarithromycin resistance, and a large-scale clinical trial is needed to choose the first-line therapy for eradication of *H. pylori* infection.

Financial support and sponsorship Nil.

Conflicts of interest

There are no conflicts of interest.

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