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Original article

Comparison of levofloxacin-containing sequential and standard triple therapies for the eradication of *Helicobacter pylori*

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ABSTRACT

Background: There is an important concern about the success of standard triple treatment for *Helicobacter pylori* (*H. pylori*) in recent years. Better eradication rates have been reported with sequential treatment in current studies. This study aimed to compare the success of a novel levofloxacin-containing sequential regimen with standard triple therapy.

Methods: H. pylori-positive patients with non-ulcer dyspepsia were randomly allocated to one of the study groups. The patients on sequential arm were given esomeprazole 40 mg BID and amoxicillin 1 g BID for the first week followed by esomeprazole 40 mg BID, levofloxacin 500 mg QD and metronidazole 500 mg TID for the second week. The patients on standard triple arm were given esomeprazole 40 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID for 2 weeks. Eradication was assessed by urea breath test on 6th weeks.

Results: Seventy-five patients were enrolled in each group; 72 in sequential arm and 67 in standard arm completed the protocols. *H. pylori* eradication rate of per protocol was 90% in sequential versus 57% in standard treatment groups with a statistical significance ($p<0.000$). Both regimens were similarly well tolerated and side effects were comparable. Only one patient in sequential arm stopped the treatment because of side effects.

Conclusion: The levofloxacin-containing sequential therapy is a significantly better strategy than the standard triple treatment for *H. pylori* eradication. Standard triple treatment is no more effective for *H. pylori* in our population and levofloxacin-containing sequential regimen might be used as a first-line eradication option.

1. Introduction

Cure of *Helicobacter pylori* (*H. pylori*) is a big challenge in the era of rising antibiotic resistance. Recent studies and meta-analyses have shown that the most commonly used eradication regimen, which consist of a PPI plus amoxicillin and clarithromycin, achieve success rates less than 80% [1,2]. An epidemiological analysis of *H. pylori* eradication studies showed a significant decrease of cure rate down to 60% with standard triple regimen in our population [3]. So, some recent data shows that standard triple therapy should no longer be considered as a first-line therapy in many geographical areas unless its efficiency is reconfirmed [4]. Sequential treatment has been suggested as an important alternative approach for *H. pylori* eradication in recent years [5]. The success rate of this novel approach was better than triple treatment in most of the controlled studies [6,7].

Levofloxacin is a synthetic fluoroquinolone which shows a significant activity on *H. pylori* both in vitro and in vivo studies. Levofloxacin has been used successfully in rescue therapies of *H. pylori*, and also in the first-line triple therapies instead of clarithromycin [8–10]. A meta-analysis of 11 randomized controlled studies showed that levofloxacin-based first-line triple therapy was more effective than standard triple therapy for eradication of *H. pylori* [11]. However, the number of studies evaluating its role on sequential regimen which replaced with clarithromycin is very limited and no study compared such a novel regimen with standard triple treatment for *H. pylori* eradication. The primary aim of this study was to compare the efficacy of levofloxacin-containing sequential regimen with standard triple treatment in the first-line treatment of *H. pylori*. The secondary aim was to assess the compliance and tolerability of this novel approach.

2. Patient and methods

This study was designed as a prospective, randomized, parallel arm trial conducted in outpatient center of an academic medical center. Study group consisted of adult patients with *H. pylori* positive

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non-ulcer dyspepsia and naive to *H. pylori* treatment. The patients who met the inclusion criteria were first screened for the *H. pylori* by ^{14}C Urea Breath Test (UBT) and then underwent an upper endoscopy and biopsy if they were positive on UBT test (Helicap, Heliprobe analyzer, Noster System AB Stockholm). The breath samples were analyzed with a validated standard method [12]. The biopsies were taken from both antrum and corpus, and after the standard procedures, *H. pylori* colonization and activity of gastritis were graded according to updated Sydney system on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe [13]. The patients who were *H. pylori* positive on both UBT and histological examination were enrolled to the study if they gave their informed consent. The principal exclusion criteria from the trial were pregnancy, lactation, gastric surgery, previous attempt of *H. pylori* eradication, liver or renal failure, consumption of PPI, Histamin-2 receptor blockers, antibiotics, bismuth salts in the last 4 weeks. The study was approved by the local ethics committee, and conducted according to the Declaration of Helsinki and the guidelines for Good Clinical Practice.

After the enrollment procedure, the patients were randomized into two parallel treatment groups with a 1:1 ratio using random sampling numbers. The first group of subjects were administered a 14-day sequential regimen consisting of esomeprazole 40 mg BID and amoxicillin 1 g BID for the first week followed by esomeprazole 40 mg BID, levofloxacin 500 mg QD and metronidazole 500 mg TID for the second week. The second group was given the standard 2-week triple therapy consisting of esomeprazole 40 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID (EAC). For both groups esomeprazole was prescribed before breakfast and dinner, all antibiotics were after meals. The details of the protocol and the importance of adherence were explained by the study physicians, and all subjects were asked to inform the study physicians for any query and any unexpected effect which can be attributed to the study drugs during the treatment. At the end of the therapy all patients were evaluated for their compliance to protocols and also questioned for any adverse effects. Compliance was assessed by pill count and defined as OK if more than 80% of drugs had been taken. Adverse effects were evaluated by study physicians and were scored as mild, moderate or severe according to their effect on daily activities. No antibiotics, PPI or histamine-2 receptor antagonists were allowed before control UBT test, but antacids only were permitted on demand. A control UBT test was performed 6 weeks after the end of treatment and successful eradication was defined as a negative UBT test.

2.1. Statistical analyses

The number of patients required in each study arm was calculated to detect a difference of 22.5% in the eradication rates between 2 protocols (Fisher exact test). Based on a two-sided test, a significance level of 5%, and a power of 0.8, at least 70 patients per group were required. Results include the binominal 95% lower and upper confidence intervals (CI). Wilcoxon rank sum test was used to compare demographic and clinical features of study groups. ITT and PP eradication rates were compared with χ^2 test with a Yates correction and the Fisher exact test when required. $p<0.05$ was considered statistically significant.

3. Results

Patients were screened and enrolled to study from January 2009 to March 2010. A total of 347 patients were screened and 150 patients randomized to study arms to receive treatment. The excluded patients were either *H. pylori* negative or did not give their consent for the study. The patients in both treatment arms were of comparable demography (Table 1). Two patients in sequential group and eight patients in EAC group were excluded due to protocol violations. Only a patient in sequential group stopped the drugs for adverse effect. As a result, 72 patients on sequential and 67 patients on EAC groups completed their regimens and made up the per protocol population. Sixty-five of 72 patients (90.2%, 95% CI 83–96) in sequential group were *H. pylori* negative at control, whereas only 34 of 67 patients (50.7%, 95% CI 44–57) were negative in EAC group. The eradication rates were significantly better in sequential group compared to EAC group both on ITT (86.6% vs. 45.3%, $p=0.000$) and on PP analyzes (90.2% vs. 50.7%, $p=0.000$) (Fig. 1). Univariate analyses showed no significant effect of age, sex, smoking, alcohol consumption, antacids use or gastritis score on the eradication rates. A total of 22 (14.6%) patients reported side effects, such as nausea (7 pts), metallic taste (6 pts), diarrhea (5 pts), abdominal pain (4 pts), vomiting (2 pts) and rash (1 pts), attributed to study drugs. But only one patient in sequential group stopped treatment because of severe nausea, vomiting and abdominal pain at second week of treatment. The symptoms resolved rapidly and the patient was asymptomatic on third day. In all remaining subjects, the side effects were generally mild or moderate and resolved in 1–5 days after the end of treatment. The frequency of side effects was not statistically significant between the groups ($p>0.05$).

Table 1
Baseline demographic and anthropometric data of the groups.

Characteristics	Sequential group	EAC group	*p*
Number of patients	75	75	
Median age (range), year	43 (19–65)	41 (20–67)	NS
Male/female	43/32	39/36	NS
Median weight, mean (kg)	77	75	NS
Median body mass index	24.2	24.6	NS
Smoking (>5 cigarette/day),	26	21	NS
Alcohol use (>1 day/week)	8	6	NS
Antacids (as needed)	18	15	NS
Gastritis score, mean (SD)	1.88 ± 0.5	2.03 ± 0.4	NS

NS: non-significant.

4. Discussion

The most commonly used treatment regimen for *H. pylori* in all over the world is the combination of a PPI with amoxicillin and clarithromycin. However, current data shows that this regimen is no more effective for eradication in many populations mostly related to raising clarithromycin resistance. A recent Japan study evaluated the change of primary resistance to clarithromycin from 1997 to 2008. It showed that the resistance rate rose from 8.7% to 34.5% during this period and the eradication rate on triple therapy decreased significantly consistent with raising clarithromycin resistance [14]. Clarithromycin resistance was found as 24.2% in a study conducted on 1999–2001 in our country [15]. However, two recent studies reported 48.2%

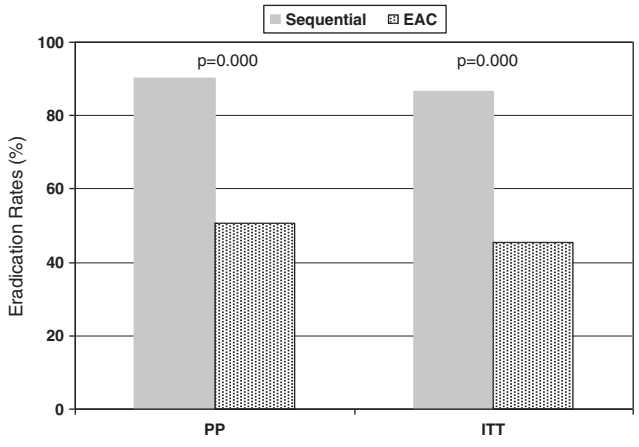

Fig. 1. The 'per protocol' and 'intention to treat' eradication rates among groups.