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Alimentary Tract

Comparison of efficacy and safety of levofloxacin-containing versus standard sequential therapy in eradication of *Helicobacter pylori* infection in Korea

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ABSTRACT

Background: Declining of eradication rates for *Helicobacter pylori* in Korea may be partly from the increasing prevalence of antibiotic resistance, especially clarithromycin resistance.
Aim: To compare the efficacy and the safety of using 10-day standard sequential therapy and levofloxacin-containing sequential therapy as a first-line treatment for *Helicobacter pylori* eradication in Korea.
Methods: A total of 200 patients with proven *Helicobacter pylori* infection randomly received 10-day standard sequential therapy ($n = 100$) or levofloxacin-containing sequential therapy ($n = 100$). The standard sequential therapy group received rabeprazole and amoxicillin for 5 days, followed by rabeprazole, clarithromycin, and metronidazole for 5 more days. The levofloxacin-containing sequential therapy group was treated with rabeprazole and amoxicillin for 5 days, followed by rabeprazole, levofloxacin, and metronidazole for 5 more days.
Results: Intention-to-treat eradication rates were 79.0% and 78.0% for groups of standard sequential and levofloxacin-containing sequential therapy, respectively ($P = 0.863$). Per-protocol eradication rates were 84.9% and 81.3%, respectively, for these two therapies ($P = 0.498$). There were no significant differences between the groups in regard to the eradication rates and adverse events.
Conclusions: The 10-day levofloxacin-containing sequential regimen and the standard sequential regimen showed the similar eradication rates of *Helicobacter pylori* in Korea.

1. Introduction

Although prevalence of *Helicobacter pylori* (*H. pylori*) infection, a cause of peptic ulcer disease, gastric adenocarcinoma, and low-grade gastric mucosa associated lymphoid tissue (MALT) lymphoma has been declining due to improved sanitation and better living conditions, the rate of failure of eradication has been increasing due to the prevalence of antimicrobial-resistant *H. pylori* strains [1–5]. These days, the standard triple therapy recommended and used as a first-line therapy for the eradication of *H. pylori* in many guidelines, including in the Korean guidelines, presented an unfavourable efficacy of less than an 80% eradication rate worldwide [6–11]. Similarly, the clinical efficacy of eradication with triple therapy seems to be unacceptable in the Korean population [12,13].

The prevalence of resistance to clarithromycin and metronidazole has increased substantially in recent years [14–16]. The Maastricht III Consensus suggested that clarithromycin should not be used in areas with a clarithromycin resistance rate >15%, and indicated bismuth-containing quadruple therapy as the first-line regimen for *H. pylori* eradication in this setting [9]. Recently, sequential therapy has been introduced. This novel therapy starts with a simple double regimen of a proton pump inhibitor (PPI) plus amoxicillin for 5 days, followed by a triple regimen of a PPI, clarithromycin, and tinidazole for the next 5 days. Several randomized studies, including meta-analysis, indicated the sequential regimen to be more efficient compared with the standard triple

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therapy [17–19]. In addition, it has also been reported that a regimen focusing on levofloxacin, a broad-spectrum fluoroquinolone that inhibits deoxyribonucleic acid (DNA) gyrase, was effective in first and second line treatment [20–22]. Considering the rapid increase in primary resistance to clarithromycin in Korea, a levofloxacin-containing regimen can be one of the therapeutic alternatives [23,24]. Recent studies about the levofloxacin-containing sequential therapy showed that this regimen was more effective in an area with >15% prevalence of clarithromycin resistant *H. pylori* strains [25,26].

Although the new levoflaxacin-containg therapy shows promise, there are doubts whether this regimen may also be effective in the Korean population because of a rise in the prevalence of fluoroquinolone resistance associated with the increasing use of fluoroquinolones in clinical practice [27,28]. In the present study, we aimed to compare the 10-day standard sequential and levofloxacin-containing sequential regimens for *H. pylori* eradication in Korea, with high resistance rates to levofloxacin, as well as clarithromycin.

2. Materials and methods

2.1. Study design

This study was conducted at Severance Hospital in Korea from January 2013 to December 2013. In the study, dyspeptic patients aged 18–76 years with *H. pylori* infection were enrolled. The presence of *H. pylori* was defined as positive if the results of one of the following two tests were positive: (1) rapid urease test (CLO^{TM}, Delta West, Bentley, Western Austria); (2) histology. Biopsy specimens, obtained by endoscopy, were fixed in formalin and used for determination of *H. pylori* infection by Giemsa staining. The exclusion criteria included: (1) patients with previous *H. pylori* eradication therapy; (2) patients treated with H2 receptor antagonist, PPI, and antibiotics in the previous 4 weeks, or nonsteroidal anti-inflammatory drug (NSAID) in the previous 2 weeks; (3) pregnant or lactating women; (4) patients who suffered from serious diseases such as severe liver disease, renal disease, and cerebrovascular disease; (5) patients who had a drug allergy to the study drugs; and (6) patients with previous gastric surgery. The study protocol was carried out in accordance with the Declaration of Helsinki, Good Clinical Practices, and was approved by the Institutional Review Board. Written informed consent was obtained by all participants. This study was registered with UMIN-CTR, identification number UMIN000015375.

2.2. Randomization and therapeutic regimens

This study was designed as a randomized, open-label, and double-arm trial. Each eligible patient was randomized to one of the two groups. A random number table was used for the random allocation of patients into the two treatment groups, by a research assistant. One group was treated with standard sequential therapy (SST) (i.e., rabeprazole 20 mg twice daily + amoxicillin 1 g twice daily for 5 days, followed by rabeprazole 20 mg twice daily + clarithromycin 500 mg twice daily + metronidazole 500 mg twice daily for five more days). The second group was treated with levofloxacin-containing sequential therapy (LST) (i.e., rabeprazole 20 mg twice daily + amoxicillin 1 g twice daily for 5 days followed by rabeprazole 20 mg twice daily + levofloxacin 250 mg twice daily + metronidazole 500 mg twice daily for five more days).

Table 1
Demographic, clinical characteristics, and endoscopic findings of the patients.

Characteristics	SST group	LST group	*p*-value
No. patient	100	100	
Age (mean ± SD), years	46.1 ± 10.5	45.0 ± 9.4	0.449
Male gender, *n* (%)	55 (55)	57 (57)	0.776
Body-mass index	22.5 ± 2.1	22.4 ± 2.2	0.670
Current smoking, *n* (%)	22 (22.0)	24 (24.0)	0.737
Alcohol intake, *n* (%)	27 (27.0)	25 (25.0)	0.872
Endoscopic diagnosis, *n* (%)			0.585
Non-ulcer dyspepsia	33 (33.0)	30 (30.0)	
Gastric ulcer	31 (31.0)	27 (27.0)	
Duodenal ulcer	29 (29.0)	29 (29.0)	
Gastroduodenal ulcer	3 (3.0)	5 (5.0)	
Gastric cancer or dysplasia	4 (4.0)	9 (9.0)	
Drop-out	7 (7.0)	4 (4.0)	0.537
Follow-up loss	4 (4.0)	2 (2.0)	
Discontinued therapy	3 (3.0)	2 (2.0)	

LST, levofloxacin-containing sequential therapy; SST, standard sequential therapy; SD, standard deviation; SST group, rabeprazole + amoxicillin for 5 days, followed by rabeprazole + clarithromycin + metronidazole for five days; LST group, rabeprazole + amoxicillin for 5 days, followed by rabeprazole + levofloxacin + metronidazole for five days.

2.3. Follow-up protocol

Patients were interviewed at completion of the therapy to assess adherence to the therapeutic regimen and adverse events. The severity of adverse effects was classified as no side effects; mild side effects; moderate; and severe. 13C-UBT, a noninvasive, nonradioactive method which is considered the gold standard in monitoring *H. pylori* status after eradication therapy, was performed in this study.

The primary outcome of the study was the eradication rate of *H. pylori* infection with SST and LST. The secondary outcomes were to assess drug adherence and the frequency of adverse events of the two different eradication regimens.

2.4. Statistical analysis

Based on previous studies about SST in Korea and LST, we assumed that SST and LST would achieve eradication rates of 79.3% and 96.0%, respectively [25,29]. Thus, to determine the 17% difference, 99 patients in each group were required with a power of 90% at a 5% significance level, with the expectation of a drop-out rate of 10%. Numerical variables were expressed as mean standard deviation (SD) or median (range) where appropriate, and categorical variables as percentages. Both intention-to-treat (ITT) and per-protocol (PP) analyses were used for the assessment of the eradication rates of *H. pylori* infections in the two groups. The ITT analysis included all randomly assigned patients who had taken at least one dose of the study medications. The PP analysis was limited to patients who took >90% of the study medications and completed follow-up. Statistical analysis of the results was performed using a chi-square test, Student's *t*-test and Fisher's exact test. For all analyses, *P* values <0.05 were considered significant. The 95% confidence intervals (CIs) were calculated by normal approximation. The analysis was performed using SPSS for Windows (version 21; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patients

Fig. 1 shows the flow of patients through the study. A total of 246 patients were screened during the study period. Among these patients, 46 did not meet the inclusion/exclusion criteria, and thus, 200 were randomized into the SST ($n = 100$) and LST ($n = 100$) groups. As shown in Table 1, the demographics and clinical