

ORIGINAL ARTICLE

헬리코박터 파이로리 치료 실패 후 레보플록사신을 이용한 3차 구제요법의 기간에 따른 제균율

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Eradication Rate by Duration of Third-line Rescue Therapy with Levofloxacin after *Helicobacter pylori* Treatment Failure in Clinical Practice

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Background/Aims: This study evaluated the eradication rate of levofloxacin-containing rescue therapy by treatment duration in patients in whom previous first- and second-line treatment failed.

Methods: Fifty-five patients with persistent *Helicobacter pylori* infection after first-line therapy and second-line therapy were studied in a single referral academic center. We compared the eradication rates by the treatment duration of third-line therapy.

Results: Of 55 patients, 12 (21.8%) received rescue therapy for seven days, 24 (43.6%) received rescue therapy for 10 days, and 19 (34.5%) received rescue therapy for 14 days. The eradication rates of therapy with levofloxacin were 65.5% in the 55 enrolled patients and 73.5% in the 49 patients who underwent follow-up testing. In cases where follow-up testing was performed, the eradication rate of 7-day therapy was 58.3%, of 10-day 68.2%, and of 14-day therapy 93.3%. Eradication rate of 14-day therapy was higher than 7-day ($p=0.06$) and 10-day ($p=0.108$), but chance could not be ruled out in the difference among groups.

Conclusions: This study showed somewhat increasing of *H. pylori* eradication rate by extending the duration of levofloxacin-containing rescue therapy to 14 days. (Korean J Gastroenterol 2016;68:260-264)

Key Words: *Helicobacter pylori*; Eradication; Levofloxacin; Rescue therapy

INTRODUCTION

The eradication rate of the triple standard therapy consisting of proton pump inhibitors (PPI), amoxicillin, and clarithromycin for *Helicobacter pylori* has been declining due to increased antibiotic resistance incidence.¹⁻⁴ For rescue therapy, bismuth-based quadruple or quinolone-based triple reg-

imens can be considered in persistent *H. pylori* infections, even after first-line therapy.^{5,6} The Korean College of *Helicobacter* and Upper Gastrointestinal Research recommends a bismuth-based quadruple regimen as a second-line therapy in case of failure after clarithromycin-containing triple therapy.⁶ If second-line treatment fails to eradicate *H. pylori*, a tailored treatment based on a bacterial culture test can

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be recommended as rescue therapy for persistent infection. However, culture for antibacterial susceptibility is not widely performed as it is time-consuming and costly.⁷ Fluoroquinolone-based therapy has been used as an alternative, but the rate of eradication differs according to dose, form of fluoroquinolone administered, and treatment duration.⁸⁻¹¹ This study evaluated the eradication rate of a levofloxacin-based regimen as third-line therapy according to treatment duration.

SUBJECTS AND METHODS

1. Patients

From 2007 to 2014, 55 patients who presented with persistent *H. pylori* infections after first treatment with standard triple therapy (PPI standard dose twice per day, amoxicillin 1 g twice per day, clarithromycin 500 mg twice per day for seven days) and second treatment with bismuth-based quadruple therapy (PPI standard dose twice per day, metronidazole 50 mg three times per day, bismuth 120 mg four times per day, tetracycline 500 mg four times per day for 7-14 days) at Soonchunhyang University Bucheon Hospital were selected for review. Levofloxacin-containing triple therapy (PPI standard dose twice per day, levofloxacin 500 mg once per day, amoxicillin 1 g twice per day) was used as a rescue third-line eradication regimen. We evaluated the eradication rate by treatment duration of third-line therapy. This study was approved by the Institutional Review Board of our institution (SCHBC 2015-04-008-002).

2. *H. pylori* eradication and assessment

Eradication was assessed by the rapid urease test (RUT), the urea breath test (UBT), or histology, four to eight weeks after completing third-line therapy. The RUT using Ponto Dry[®]

(Gastrex, Gilly les Citeaux, France) was interpreted as positive if there was a color change of the yellow gel to pink or red one hour after examination. The UBT was performed in overnight fasted patients. An initial breath sample was obtained to establish a baseline ratio of ¹³CO₂ to ¹²CO₂. The patient then ingested a tablet of 100 mg urea labeled with ¹³C (UBIT[®]; Korea Otuska Pharm, Seoul, Korea). A second breath sample was taken after 15 minutes. All breath tests were analyzed using an infrared spectrophotometer (UBiT[®]-IR300; Otsuka Electronics Co., Ltd, Osaka, Japan). A difference in the ratios > 2.5‰ was considered positive. If *H. pylori*, a spiral-shaped bacterium, was found in H&E staining, special staining using modified Giemsa stain, or Warthin-Starry silver stain, histology was considered positive.

3. Eradication rate after third-line rescue therapy

Eradication rate was evaluated in all enrolled patients as well as in the patients who underwent follow up tests (RUT, UBT, or histology). To evaluate the efficacy of treatment duration extension, the enrolled patients were assigned to one of three treatment lengths: seven days, 10 days, or 14 days, and patients that underwent testing after eradication were assigned to a subgroup. In addition, tolerability was evaluated based on the number of patients who underwent follow-up testing after completion of third-line therapy.

4. Statistical analysis

Categorical data were compared among groups using a chi-square or Fisher's exact test. The analyses were carried out using the SPSS for Windows software package (ver. 14.0, released 2005; SPSS Inc., Chicago, IL, USA). Continuous data were presented as means±SDs, and were compared using one-way analysis of variance with Tukey's *post-hoc* test

Table 1. Baseline Characteristics of Enrolled Patients

Characteristic	Total (n=55)	7-day group (n=12)	10-day group (n=24)	14-day group (n=19)	p-value
Age (yr)	57.4±12.1	54.8±13.7	59.3±12.4	56.7±10.9	NS*
Sex, male/female	27 (49.1)/28 (50.9)	5 (41.7)/7 (58.3)	12 (50.0)/12 (50.0)	10 (52.6)/9 (47.4)	0.884
Disease					0.231
Gastric ulcer	38 (69.1)	7 (58.3)	19 (79.2)	12 (63.2)	
Duodenal ulcer	16 (29.1)	4 (33.3)	5 (20.8)	7 (36.8)	
<i>Helicobacter pylori</i> gastritis	1 (1.8)	1 (8.3)	0 (0)	0 (0)	
Follow-up	49 (89.1)	12 (100)	22 (91.7)	15 (78.9)	0.151

Values are presented as mean±SD or n (%).

*No significant differences between groups (p > 0.05).

applied. Null hypotheses of no difference were rejected if p-values were less than 0.05. Eradication rate was calculated as a percentage of total enrolled patients in each group, with 95% CIs.

RESULTS

1. Baseline characteristics

Fifty-five patients treated with a levofloxacin-containing triple rescue regimen due to failure of first- and second-line treatment for *H. pylori* were selected for review. The mean age of enrolled patients was 57.4 ± 12.1 years, and 69.1% of patients were diagnosed with gastric ulcers, 29.1% with duodenal ulcers, and 1.8% with *H. pylori* gastritis. Among these patients, 12 (21.8%) received 7-day therapy, 24 (43.6%) received 10-day therapy, and 19 (34.5%) received 14-day therapy. There were no significant group differences in mean age, ratio of gender, or indication of eradication (Table 1).

2. Eradication rate and tolerability

In the 55 selected patients, the eradication rate was 65.5% (95% CI, 0.513-0.774). The eradication rate of the

7-day therapy was 58.3% (95% CI, 0.286-0.835), of 10-day therapy 62.5% (95% CI, 0.408-0.805), and of 14-day therapy 73.7% (95% CI, 0.486-0.899) ($p=0.625$). The eradication rate of the 14-day therapy was not significantly different from that of the 7-day group ($p=0.447$) (Table 2).

Among the total 55 patients, no patients from the 7-day group, two (8.3%) patients from the 10-day group, and four (21.1%) patients from the 14-day group did not have further visits recorded in their charts and did not undergo the UBT, the RUT, or endoscopy ($p=0.206$) (Fig. 1). In the group that underwent later testing, the total eradication rate was 73.5% (95% CI, 0.587-0.846). The eradication rate in the 7-day group was 58.3% (95% CI, 0.286-0.835), in the 10-day group 68.2% (95% CI, 0.451-0.853), and in the 14-day group 93.3% (95% CI, 0.660-0.997) (Table 2). Eradication rates after 14 days of treatment were significantly higher than the 7-day rates ($p=0.06$), but chance could not be ruled out in the difference between 14 days and 10 days ($p=0.108$).

DISCUSSION

This retrospective study investigated the eradication rate of levofloxacin-containing triple therapy in clinical practice and assessed the efficacy of different treatment lengths. In patients who underwent follow-up testing, eradication rates were 58.3% for 7-day therapy, 68.2% for 10-day therapy, and 93.3% for 14-day therapy. As treatment duration was extended, the rate of eradication increased; however, this increase was not statistically significant. Unfortunately, the number of patients that did not continue regular exams was highest in the 14-day group. This data suggests that compliance is important to increase the rate of eradication in patients undergoing a levofloxacin-containing triple regimen as rescue therapy.

Table 2. Eradication Rate according to Duration of Third-line Rescue Treatment

Treatment duration	Eradication rate	
	Enrolled patients (total, n=55)	Subgroup (follow-up, n=49)
7-day group	58.3 (0.286-0.835)	58.3 (0.286-0.835)
10-day group	62.5 (0.408-0.805)	68.2 (0.451-0.853)
14-day group	73.7 (0.486-0.899) [†]	93.3 (0.660-0.997) [‡]
Total	65.5 (0.513-0.774)	73.5 (0.587-0.846)

Values are presented as % (95% CI).

[†] $p=0.447$ compared with 7-day group, [‡] $p=0.06$ compared with 7-day group.

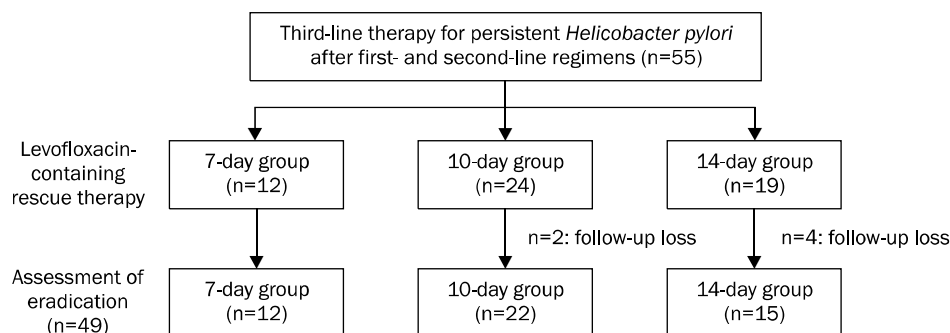


Fig. 1. Study flowchart.

Conventional triple therapy of clarithromycin, amoxicillin, and PPI is accepted as the first-line treatment choice in many countries, including Korea.^{6,12} However, many factors, including bacterial resistance to antibiotics, poor patient compliance, and cytochrome 2C19 polymorphism, influence the failure of eradication for *H. pylori*.^{13,14} The eradication rate of conventional triple therapy is reported at less than 80%, and it is not recommended for first-line treatment in areas where the population clarithromycin resistance rate is over 20%.⁵

As bacterial resistance is increasing and the eradication rate of first-line therapy is declining,^{15,16} rescue therapy to treat persistent infections, even after first- or second-line therapy, is needed.^{17,18} The Korean College of *Helicobacter* and Upper Gastrointestinal Research recommends bismuth-based quadruple regimen therapy or a regimen including two or more antibiotics excluding metronidazole or tetracycline, which are used in first-line therapy and as second-line rescue therapy.⁶ However, strategies for third-line rescue have not been determined in Korea, although Asia-Pacific guidelines recommend testing for CYP2C19 polymorphism, and the Maastricht IV/Florence guidelines recommend testing for antibiotic resistance in first- and second-line regimen failure.^{5,17,19}

In clinical practice, quinolone-based triple therapy is used widely as rescue therapy. Gisbert et al.²⁰ reported that bismuth- and levofloxacin-containing quadruple therapy had an eradication rate of >90% as a second rescue therapy, whereas Jeong et al.²¹ showed that the eradication rate of levofloxacin-based third-line therapy (500 mg, once or twice per day for 10 days) was 57.1% in 14 patients. The eradication rates of quinolone-based rescue therapy vary according to treatment duration, form and dose of quinolone, and bacterial resistance to quinolone.^{11,22-27} Resistance to fluoroquinolone is increasing in Korea^{28,29} and a 7-day quinolone regimen had a low eradication rate (51.6-69.8%).³⁰⁻³² A 10-day quinolone regimen has been used as rescue therapy,³³⁻³⁷ but extension of treatment to 14 days seemed to improve the rate of eradication.^{26,38} Our study demonstrated that extension of duration of levofloxacin-based rescue regimen improved the eradication rate, although quinolone resistance is increasing worldwide.³⁹⁻⁴¹ Moreover, it is important to note that exposure to quinolone can delay tuberculosis and bacterial resistance diagnosis.^{38,42} In addition, prolonged treatment can result in adverse effects such as

metallic taste, nausea, or diarrhea.³⁵ In this study, follow-up loss increased as treatment duration was extended. However, we cannot conclude that the loss resulted from adverse events due to extended treatment, as insufficient information was included in the retrospective data we utilized.

This study had several limitations. First, a small number of patients were selected, as only cases with persistent *H. pylori* after first- and second-line therapy were included. Second, this study provided no details of adverse events associated with extended quinolone treatment. Third, third-line rescue therapy was adopted empirically in a clinical setting and it was not based on cases of bacterial resistance. Additionally, there were no guidelines for treatment duration choice. Lastly, there is a possibility of eradication rate overestimation, as we considered *H. pylori* eradicated if negative findings were detected on one or more serial tests.

In conclusion, this study showed a slightly increasing *H. pylori* eradication rate by extending the duration of levofloxacin-containing rescue therapy to 14 days. However, a large-scale prospective study is required to evaluate the adverse effects related to prolonged treatment duration of quinolones.

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