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Efficacy of Rifaximin Add-On Levofloxacin Regimen as Third-Line Rescue Therapy of Helicobacter Pylori Eradication

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Helicobacter pylori; Eradication; Rescue therapy; Introduction

1. Abstract

1.1. Background/Aims

Levofloxacin–amoxicillin triple therapy was known as a choice of third-line regimen for Helicobacter pylori (H. pylori) eradication. But it does not achieve the satisfactory eradication success rate. The objective of this study was to determine the efficacy of rifaximin add-on levofloxacin regimen.

1.2. Method

We performed retrospective, observational study from June 2017 to June 2020. The patients treated for 14 days as third-line rescue therapy were enrolled. Those patients had experienced treatment failure of two consecutive times of H. pylori eradication therapies, which were standard triple therapy as first-line therapy and bismuth based quadruple regimen as second-line therapy. The patients were divided in the two group: PPI, amoxicillin, levofloxacin and rifaximin (PAL-R) and PPI, amoxicillin, levofloxacin (PAL) regimen. The 13C- urea breath test was performed at least 4 weeks after the completion of eradication therapy. We compared the eradication rate of the PAL-R and PAL therapy.

1.3. Results

Total 53 patients received the third line regimen. Among them. 29 patients were treated with PAL-R regimen and the eradication rates was 80.8% (21 of 26 patients) in per protocol analysis. During the same period, a total of 24 patients were treated with 14day PAL regimen and the eradication rate was 52.4% (11 of 21 patients). The eradication rate achieved with the PAL-R regimen was significantly higher than that with the PAL regimen in intention to treat (P=0.05) and per protocol analysis (P=0.03).

1.4. Conclusion

Rifaximin add-on PAL(PAL-R) regimen could be used effectively as third-line rescue therapy of H. pylori eradication.

2. Introduction

Helicobacter pylori (H. pylori) is a common bacterium that affects more than half of the world's population [1,2]. Approximately 15% of the infected people develop peptic ulcers, about 1% of them or less could cause stomach cancer during their lifetime [3]. It is also known to be associated with hematologic diseases such as gastric MALT (mucosa-associated lymphoid tissue) lymphoma, immune thrombocytopenia, and iron deficiency anemia [4-6]. Since clarithromycin based standard triple therapy was introduced in 1980's, eradication rates for H. pylori infection was in excess of 90% in the early 2000's. As recently as 2020's, about 20% of patients failed eradication, even after the administration of standard triple therapy and second line bismuth based quadruple therapy [7] Several rescue regimens would have been designed, but significant portion of the patients failed the eradication of H. pylori [8]. Levofloxacin based triple therapy is well known choice of third-line regimen, but it has not yet shown a satisfactory eradication success [9]. In a study that analyzed six European cohort studies with levofloxacin based triple therapy as a third-line regimen, the mean eradication rate was 73% [10]. There

were studies showing that the eradication period of 10 days or longer is more effective, but there are few studies on third line therapy [8]. Furthermore, antibiotic resistance to levofloxacin is also increasing, like other antibiotics. According to the recently published systemic review, there was a tendency to increase the resistance to levofloxacin over the years [11] In particular, levofloxacin resistance was 29% in Southeast Asia and 31% in the Western pacific region in 2012-2016. It is concerned that the effectiveness of levofloxacin triple therapy would be decreasing as resistance to levofloxacin increases. In recent studies of Korea and Japan studies for the levofloxacin based triple regimen as a third-line regimen, the eradication rates were relatively low (43-57%) [12,13]. Rifaximin is one of the rifamycin derivatives and also has an antimicrobial effect on H. pylori. Since this drug is hardly absorbed by the gastric and intestinal mucosa, it maintains high concentration in the gastrointestinal tract and has a little systemic adverse effect [14]. Therefore, Rifaximin is mainly used in gastrointestinal infections, and it could be expected to be effective in H. pylori eradication treatment. Unfortunately, there were limited data for the efficacy of rifaximin-added regimen. In this study, we aimed to compare the rifaximin add-on levofloxacin regimen as a third-line regimen with traditional levofloxacin triple therapy.

3. Methods

3.1. Study Design

The retrospective observational study was approved by the Ethics Committee of the Catholic University of Korea (VC20RISI0200). The authors reviewed the electronic medical chart of patient who received the third line rescue therapy at the St. Vincent's Hospital, the Catholic University of Korea from June 2017 to June 2020. The data abstracted including age, gender, first and second line H. pylori eradication regimens therapy, a history of pretreatment with a PPI or histamine-2 receptor antagonist (H2RA), endoscopic findings, and adverse events. All patients underwent esophagogastroduodenoscopy prior to eradication therapy. And all patients who received the the first line H. pylori eradication regimens therapy (proton pump inhibitor (PPI), amoxicillin, and clarithromycin for 14 days) and second line quadruple regimen (PPI, bismuth, tetracycline, and metronidazole for 7 days) were included this study. H. pylori infection was diagnosed by the rapid urease test (CLO test) or the initial biopsy (Warthin–Starry stain), and treatment failure confirmed by the 13C-urea breath test (UBT) after at least 4weeks.

3.3. Third Line H. Pylori Eradication Regimen and Treatment Outcome

The patients were divided in the two group: PALR and PAL group.

The PALR group included the patients who received the14-days high dose PPI, amoxicillin 500 mg b.i.d., levofloxacin 250 mg b.i.d., rifaximin 400 mg t.i.d. And 14 days high dose PPI, amoxicillin 500 mg b.i.d., levofloxacin 250 mg b.i.d were used for patients of PAL group. The success rate of eradication was evaluated by intention-to-treat and per-protocol analyses. Exclusion criteria for per-protocol analysis included patients with poor compliance and patients who did not return to undergo a UBT test to assess the results of third-line therapy.

The primary outcome was the eradication rate after third line rescue therapy.

4. Statistics

For categorical variables, chi-square test or Fisher exact test was performed. Basically chi-square test was used and Fisher exact test was used only when more than 20% of expected frequencies were lower than 5. For continuous variables, Mann-Whitney test was performed. The p-values less than 0.05 were considered significant. All the statistical analyses were performed using the SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, U.

5. Results

A total of 53 patients were enrolled the third line rescue therapy for H. pylori eradication. Of them, 29 patients were treated with the PAL-R regimen, and 21 patients were treated with the PAL regimen. The baseline characteristics of each group are provided in Table 1. The mean age of patients was 63.5 ± 12.8 in the PAL group and 63.8 ± 10.6 in the PAL-R group. Males comprised 37.5% of the PAL, 55.2% of the PAL-R group. The endoscopic diagnosis of each group did not show significant differences. The PP analysis, the data of 21 patients with the PAL and 26 patients with the PAL-R regimen were analyzed. The eradication rates in intention to treat (ITT) analyses were 45.8% (11 of 24 patients) in the PAL group, 75.9% (21 of 29 patients) in the PAL-R group. (P=0.05) The eradication rates in per-protocol (PP) analyses were 52.4% (11 of 21 patients) in the PAL group, 80.8% (21 of 26 patients) in the PAL-R group. (P=0.03) The eradication rate achieved with the PAL-R regimen was significantly higher than that with the PAL regimen in PP analyses. (Figure 1) There was no significant adverse event. The overall treatment was completed successfully without any drug administration problems.

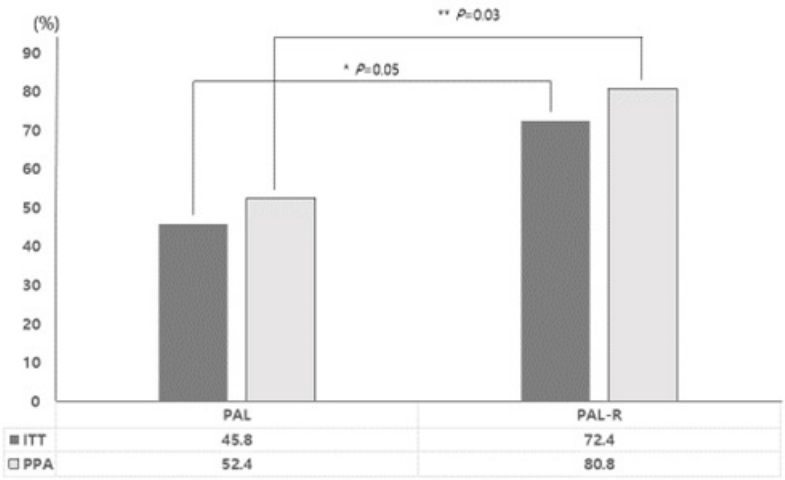

Figure 1. Eradication rate of the PALR regimen and PAL regimen. The eradication rate achieved with the PAL-R regimen was significantly higher than that with the PAL regimen in intention to treat (P=0.05) and per protocol analysis (P=0.03).

Table 1. Baseline characteristics of patients.

	PAL (n=24)	**PAL-R (n=29)**	P-value
Age, mean ± SD	63.5 ± 12.8	63.8 ± 10.6	0.909
Male, N (%)	9 (37.5%)	16 (55.2%)	0.200
Endoscopic diagnosis			
Gastric ulcer (%)	5 (20.8%)	8 (27.6%)	
Duodenal ulcer (%)	2 (8.3%)	2 (6.9%)	
Gastritis (%)	11 (45.8%)	10 (34.5%)	
Gastric adenoma (%)	3 (12.5%)	4 (13.8%)	
Early gastric cancer (%)	3 (12.5%)	5 (17.2%)	

6. Discussion

The present study demonstrated the effectiveness of rifaximin-added regimen as a third-line H. pylori rescue therapy. This was a retrospective observational study, and we comapred the efficacy of third line rescue therpy between traditional levofloxacin triple regimen with rifaximin adding regimen. There was no significant drug adverse event between the two groups, and the PALR regimen group showed successful eradication rate of more than 80%, which was significantly higher than the PAL regimen group. In South Korea, standard primary H. pylori treatment guidelines recommend clarithromycin based standard triple therapy as first-line and bismuth quadruple therapy as second-line regimen [8,15]. Up to date, there is no clear recommendation of the third-line eradication regimen, when the second treatment fails. There are several regimens currently proposed as empirical third-line eradication therapy. High-dose proton pump inhibitor (PPI) and amoxicillin combined dual therapy are proposed, because amoxicillin will be active in acid dependent manner. High dose PPI can raise intragastric pH, and more active portion of amoxicillin influence the bacterium. However, more frequent dosing (4 times per day) might reduce the patient's compliance. And in a multi-center randomized controlled study of third-line H. pylori treatment published in Japan in 2013, the eradication rate of high-dose PPI-amoxicillin dual therapy was low as 54.3% of ITT analysis and 56.7% of PP analysis [12]. Rifamycin derivatives (rifampicin, rifabutin, and rifaximin) exert antibacterial activity against H. pylori. Rifabutin has been used as a rescue therapy after failed eradication therapy. A study published in 2016 showed a high eradication rate of 81.8 to 91.7% when rifabutin triple therapy administered as third- or fourth-line rescue therapy [16]. However, rifabutin has the disadvantage that it can rarely cause serious adverse effects such as myelotoxicity. Even when rifabutin administered for the treatment of H. pylori, bone marrow toxicity reported in 1.5-3.0% [17]. Levofloxacin based triple therapy has shown quite effective and safe results [9,10]. However, the resistance of H. pylori to levofloxacin has been increasing in recent years. Especially in Korea and Japan, Levofloxacin based triple therapy showed relatively low eradication rates (43-57%) [12,13]. In the present study, the eradication rate of the Levofloxacin triple therapy group was also as low as 54.5%. Levofloxacin triple therapy is currently widely used as a third-line rescue treatment in South Korea, but this suggests that another regimen is needed to replace it. Rifaximin is also a derivative of rifamycin like rifabutin, but it is nonabsorbable, thus resulting in low blood levels. Accordingly, it does not cause serious adverse effects associated with rifabutin [14]. Rifaximin triple therapies, a combination of (clarithromycin, amoxicillin or levofloxacin) and PPI, did not show a high eradication rate as a primary treatment for H. pylori. (18, 19) And in a study that

conducted a rifaximin-based triple regimen as a third-line H. pylori treatment, the eradication rate was 65%, and the administered regimen was rifaximin, levofloxacin, and PPI triple therapy for one week [20]. But a study published in 2011 showed a considerable bactericidal effect when rifaximin was added to levofloxacin triple therapy as the primary treatment for H. pylori, with a few adverse effects [21]. Therefore, rifaximin triple therapy had insufficient effect, but when rifaximin was added to levofloxacin-amoxicillin triple therapy and used as a quadruple drug therapy, it showed significant effect. We expected that rifaximin add-on levofloxacin triple therapy would also be effective in third-line rescue therapy, and compared with conventional levofloxacin triple therapy. As for the dosing period, there is a meta-analysis that the 2-week therapy is more effective than 1-week therapy in the conventional levofloxacin triple therapy, and rifaximin add-on therapy was also administered for 2 weeks [8]. This is the first study of adding rifaximin to conventional levofloxacin triple therapy as a third line rescue therapy. In the present study, rifaximin add-on levofloxacin triple therapy was superior to thel levofloxacin triple therapy as rescue therapy. The limitation of this study is that the number of enrolled patients was small. And it was a retrospective study. In order to confirm the results of the present study, it is necessary to conduct a randomized controlled study in the future. In conclusion, this study showed that the regimen of adding rifaximin to the existing levofloxacin triple therapy in H. pylori third-line treatment was superior to the levofloxacin triple therapy. Rifaximin add-on regimen seems to be able to complement the conventional levofloxacin triple regimen in situations where levofloxacin resistance increases. Rifaximin add-on PAL regimen may be considered a third-line eradication treatment in patients who have failed standard primary and secondary treatment.

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