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헬리코박터 파일로리 감염에서 고용량 및 다빈도 덱스란소프라졸과 아모시실린 이중 치료: 단일군 전향 연구

박혜윤, 강은정, 김동근, 김기주, 최진우, 남수연, 권용환, 이현석, 전성우
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High and Frequent Dose of Dexlansoprazole and Amoxicillin Dual Therapy for *Helicobacter pylori* Infections: A Single Arm Prospective Study

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Background/Aims: Recently, the eradication rate of *Helicobacter pylori* (*H. pylori*) infection has decreased to less than 80% worldwide with the use of clarithromycin-based triple therapy owing to the increased resistance of *H. pylori* to antibiotics, especially clarithromycin and metronidazole. This prospective study aimed to determine eradication rate of *H. pylori* following high and frequent doses of extended-release dexlansoprazole and amoxicillin, as a dual therapy in a region with high clarithromycin resistance rate.
Methods: A total of 50 treatment-naïve patients with active *H. pylori* infections, who were confirmed through via rapid urease test or histology and serology between November 2015 and February 2016 at our hospital, were included for analysis. All enrolled patients were treated with 750 mg amoxicillin and 30 mg dexlansoprazole, four times a day for a total duration of 14 days. Treatment success was determined using urea breath test four weeks after treatment completion.
Results: Seven out of the 50 patients (29 men and 21 women; mean age, 57 years) dropped out during the study. The total eradication rate was 52% (26/50), and that for those with a compliance rate of over 90% was 68.4% (26/38). *H. pylori* infections were not successfully eradicated in patients with a compliance rate of less than 90%. Nine patients (18%) reported side effects, such as mild diarrhea and abdominal fullness. No significant factors, such as smoking and alcohol consumption, affected the infection the eradication rate.
Conclusions: High and frequent doses of proton pump inhibitor–amoxicillin dual therapy were not effective in eradicating *H. pylori* infection in a province with high clarithromycin resistance rate. **(Korean J Gastroenterol 2017;70:176-180)**

Key Words: Antibiotics; Resistance; *Helicobacter pylori*; Treatment

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is a well-known risk factor for various upper gastrointestinal diseases, such as gastritis, gastroduodenal ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer.[1,2] Hence, eradication of *H. pylori* infection, as a means to treat and prevent these mentioned upper gastrointestinal diseases is high important. Meanwhile, the rate of eradication of *H. pylori* infection has been decreasing to <80% recently with the use

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of clarithromycin-based triple therapy worldwide.[3-5] Such trend remains apparent in a Korean territory with increased resistance to antibiotics commonly used to eradicate *H. pylori* infection.[6,7] This increase in resistance to antibiotics previously and commonly used for the eradication of *H. pylori* is contributing to the decrease in the eradication rate. To solve this problem, new and diverse regimens have been proposed to replace the empiric first-line therapy.

Some randomized trials on concomitant versus standard therapy and sequential versus standard therapy, which were conducted at home and abroad, reported an eradication rate of less than 90% for these regimens. Additionally, a previous multicenter prospective study performed in our hospital also showed that the eradication rates for *H. pylori* infection were 87.9% and 88.7% for sequential and concomitant therapies, respectively, according to the per-protocol (PP) analysis.[8,9] These results were attributed to the increased resistance of *H. pylori* to antibiotics, especially clarithromycin and metronidazole, in our province. In the 1990s, a high-dose proton pump inhibitor (PPI)–amoxicillin dual therapy was introduced as one of the alternative first-line therapies based on the theoretical studies showing that amoxicillin has a lower incidence of resistance compared with clarithromycin or metronidazole, and that its bactericidal effect can be amplified by increasing the maximum intragastric pH using high-dose PPI.[10,11] Although previous studies that utilized high-dose PPI –amoxicillin dual therapy administered twice daily reported a cure rate for *H. pylori* infection of 50-80%, this dual therapy was not recommended as a first- or second-line treatment due to its significantly lower eradication rate compared with triple therapy.[12,13] Since then, several attempts on the use of higher and more frequent doses of PPI and amoxicillin than the previous dual therapies were made because the bactericidal effect of amoxicillin is time- and pH-dependent.[11,14] A large-scale multihospital trial showed an infection eradication rate of over 90%,[15] and this finding prompted us to validate the efficacy of high and frequent doses of PPI–amoxicillin dual therapy in our province, where the clarithromycin resistance rate is relatively high. To maintain a high intragastric pH level, we selected a long-acting PPI with intensive effect. A previous review article reported that a modified release formulation of dexlansoprazole particularly increased the percentage of time that the intra-gastric pH was greater than 4, compared with the other PPIs; based on this, we chose the extended-release dexlansoprazole in the present study.[16,17]

Our study aimed to verify the *H. pylori* infection eradication rate with high and frequent doses of extended-release dexlansoprazole–amoxicillin dual therapy through an alternative trial in a region with high rate of clarithromycin resistance.

SUBJECTS AND METHODS

1. Patients and regimen

This prospective, single-center study focused on treating patients with *H. pylori* infection who were referred to our hospital between November 2015 and February 2016. Participants were chosen among those who underwent endoscopy for screening or had upper gastrointestinal symptoms. From these participants, two biopsy specimens were obtained for rapid urease test and histology of the antrum and corpus. *H. pylori* infection was diagnosed based on the results of rapid urease test or histology with Giemsa stain, and serology. A positive *H. pylori* infection was defined as having positive results in more than two of the aforementioned tests. The exclusion criteria included previous *H. pylori* treatment; use of drugs that could influence the diagnostic test and treatment results (e.g., PPI, antibiotics, H2 receptor antagonist, and bismuth) within 2 weeks before enrollment to the study; use of concomitant drugs with steroid, aspirin, and antithrombotic agents; previous history of gastric surgery, except for endoscopic procedure; presence of severe medical conditions (e.g., heart, lung, liver, kidney, and endocrine system abnormalities); diagnosis of hematologic disease or other cancerous diseases except for early-stage gastric cancer; pregnant or lactating condition; and previous history of allergic reaction with any of the study medications.

All enrolled patients were treated with 750 mg amoxicillin and 30 mg dexlansoprazole four times daily for 14 days. Study medications were supplied in packs, and to assess for treatment compliance, patients were instructed to return all unused medications. The presence of adverse symptoms was also checked through patient's diary. The treatment outcome was assessed 4 weeks after treatment completion using ^{13}C urea breath test (UBT) (100 mg ^{13}C urea; UBiT-IR300, Otsuka Electronics, Japan) after 8 hours of fasting. The cutoff value for UBT was 2.5%. Treatment was considered successful if UBT yielded a negative result. All patients with treatment

failure in this study were administered with domestic standard second-line anti-*H. pylori* treatment as follows: full-dose PPI two times daily, 500 mg metronidazole three times daily, and 120 mg bismuth and 500 mg tetracycline four times daily for 7 days.

This study was approved by the institutional review board of our hospital (KNUMC_15-1001) and registered in the Clinical Research Information Service (cris.nih.go.kr; KCT0001758); informed consent was obtained from all participants.

2. Statistical analysis

According to the pilot study with respect to identifying a tentatively effective therapy, the PP cure rate of 90% or greater and rate of 80% or less was considered as unacceptable. A maximum of 50 patients was needed to achieve a lower 90% confidence interval (CI) of ≥80% in this study.[18] As a single-arm prospective pilot study, up to 50 patients were included. In some previous pilot studies, the stopping points were defined as follows: the study stopped if a cure rate of 97% (29 of 30; 90% CI, 80-99%) was achieved or 6 failures occurred after 30 patients. The study stopped if a cure rate of 92% (37 of 40; 90% CI, 82-98%) was achieved or 6 failures occurred after 40 patients. Lastly, the study stopped if a cure rate of 92% (45 of 50; 95% CI, 80-96%) was achieved after 50 patients.[18-20] However, we completed the enrollment of 50 patients before obtaining the result of UBT test in 30 patients. Moreover, the treatment effect of high-dose dexlansoprazole–amoxicillin dual therapy was analyzed through a PP analysis in patients with greater than 90% treatment compliance rate and intention-to-treat (ITT) analysis in a total of 50 patients at a time. The statistical calculations were performed using SPSS for Windows, version 18.0, software (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 50 patients with *H. pylori* infection were initially enrolled in the study, of whom 29 were men and 21 were women, with a mean age of 57 years. The endoscopic diagnoses showed gastric ulcers (n=8), duodenal ulcers (n=3), ulcers due to endoscopic resection for gastric adenoma or early-stage gastric cancer (n=37), and gastritis (n=2). From the total number of patients, 6 were dropped due to withdrawal of consent during the study, of whom, 1 patient was excluded due to previous history of antibiotic medication use. Thirty-three (66.0%) and 38 (76.0%) patients had a compliance rate of 100% and greater than 90%, respectively, based on pill count. Furthermore, ITT treatment success was observed in 26 out of the 50 patients (52.0%), whereas PP treatment success of those with a compliance rate of greater than 90% was observed in 26 out of the 38 patients (68.4%). *H. pylori* was not eradicated in all patients with a compliance rate of below 90%. Moreover, failure to eradicate *H. pylori* was

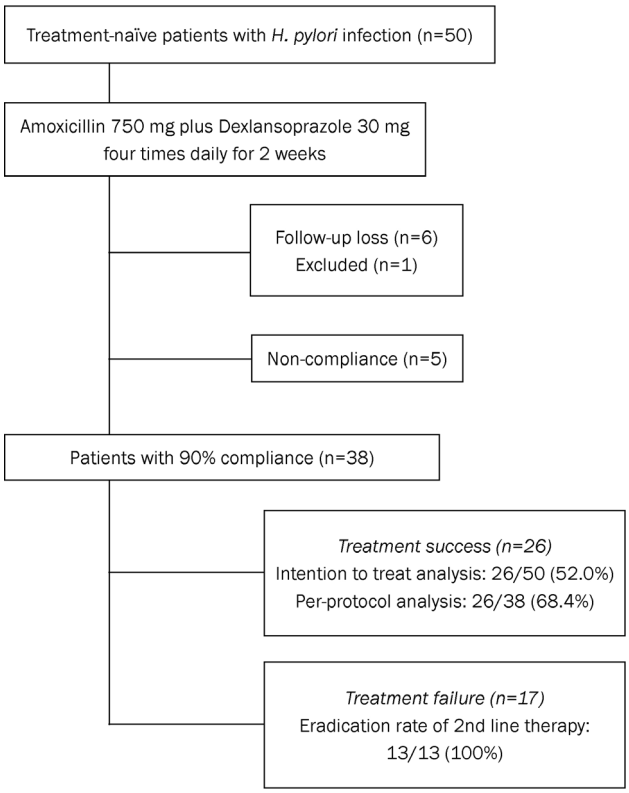

Fig. 1. Flow chart of the study. *H. pylori*, *Helicobacter pylori*.

Table 1. Side Effects of High-dose PPI–Amoxicillin Dual Therapy

Side effects	Number of complaints (n=43)
Diarrhea	3 (6.9)
Vomiting	1 (2.3)
Nausea	2 (4.6)
Glossitis	1 (2.3)
Abdominal fullness	4 (9.3)
Headache	1 (2.3)
Constipation	2 (4.6)
Itching sensation	2 (4.6)
Vaginitis	1 (2.3)
Bitter taste	2 (4.6)

Values are presented as number (%).
PPI, proton pump inhibitor.

observed in 17 patients; of which, four refused to receive the second-line therapy. Thirteen patients with treatment failures were retreated using the second-line therapy with a 100% success rate (Fig. 1). Nine patients (18.0%) reported side effects, such as diarrhea and abdominal fullness, while they only experienced mild symptoms (Table 1). No patient withdrew from the study due to side effects. No significant factors affecting the eradication rate, such as age, smoking, and underlying endoscopic diagnoses, were found.

DISCUSSION

The effectiveness of high and frequent doses of PPI–amoxicillin dual therapy is thought to be improved by the time- and pH-dependent characteristics of amoxicillin. Thus, a higher intragastric pH level as well as a greater frequency and duration of exposure to amoxicillin can increase the intragastric mucosal concentration of amoxicillin, reducing the minimum inhibitory concentration of *H. pylori*.[14,21]

Actually, studies conducted in the mid-1990s reported that the PPI–amoxicillin dual therapy administered twice daily for 2 weeks was not sufficient in increasing the cure rate compared with the standard triple therapy.[12,13] Additionally, even a recent study that utilized high-dose extended-release lansoprazole–amoxicillin dual therapy administered twice daily for 2 weeks showed an infection eradication rate of 53.8% in both ITT and PP analyses.[20] However, some studies revealed improved results with the administration of high and frequent doses of PPI–amoxicillin dual therapy, three or four times daily for 2 weeks as a first-line treatment for *H. pylori* infection. A double-blind, randomized, controlled multicenter trial in Germany reported an eradication rate of 91% in the ITT analysis with the use of high and frequent doses of dual therapy thrice daily for 2 weeks.[22] Furthermore, a multihospital trial in Taiwan reported infection eradication rates of 95.3% and 96.6% in the ITT and PP analyses, respectively, with the administration of high and frequent doses of PPI–amoxicillin dual therapy four times daily for 2 weeks as the first-line treatment.[15] Based on these studies, we expected an eradication rate of greater than 90% with the use of high and frequent doses of dexlansoprazole–amoxicillin regimen four times daily for 2 weeks in our province. However, the results did not meet our expectation.

Some previous studies also showed a low *H. pylori* eradication rate of less than 90%, even with the administration of high and frequent doses of dual therapy three or four times daily for 2 weeks as the first-line therapy, which is similar to our study. One prospective, single-center study that used high and frequent doses of dual therapy three times daily showed a low infection eradication rate (72.2% and 74.2% in the ITT and PP analyses, respectively).[19] Additionally, a randomized, controlled multicenter study in Japan revealed lower infection eradication rates (54.3% and 56.7% in the ITT and PP analyses, respectively) than those in a previous study with the administration of high and frequent doses of dual therapy four times daily.[23] Another randomized controlled study in Korea made a comparison between the dual therapy and the standard triple therapy, with both administered thrice daily. The results showed that both groups had similar eradication rates, with low *H. pylori* eradication rates of 67.3% and 78.4% in the ITT and PP analyses, respectively.[24] We attributed the negative result of our study to drug compliance, which was an important issue among participants. Only 76% of our patients had a compliance rate of greater than 90%. Similarly, the authors of other studies with low infection eradication rate, despite the use of high and frequent doses of dual therapy, also pointed to low treatment compliance as the cause of the results. We also considered other factors, except for PPI dose frequency, that could influence the intragastric pH level, such as CYP2C19 and IL-1β genotypes in some patients. Some studies showed that high-dose PPI could effectively increase the intragastric pH level in refractory *H. pylori*-infected patients with CYP2C19 extensive metabolizer genotype.[21,25] Lastly, other mechanisms involved in the resistance of *H. pylori* to amoxicillin might affect the result of this study, despite the time-dependent bactericidal effect of this drug. Specifically, the production of beta-lactamase, loss of affinity between amoxicillin and penicillin-binding protein transpeptidase through multiple point mutations in penicillin-binding protein 1 gene, as well as alterations in the membrane permeability through channels and penicillin-binding protein 1 mutations are perhaps the reasons for the increased resistance of amoxicillin to *H. pylori*.[26]

Our study has some limitations to consider when interpreting the results. First, this single-center study enrolled only a small number of patients, which may be attributable to the lower *H. pylori* eradication rate in our study compared with

other previous studies that utilized high and frequent doses of dual therapy. However, the performance of a large-scale clinical trial of the same kind is not necessary in our country because insignificant result is highly expected. Second, no processes were established in our study to confirm whether *H. pylori* among the enrolled patients were resistant to amoxicillin. However, although previous studies identified amoxicillin resistance as a factor in the low infection eradication rate, it is considered to have no direct effect on the result of our study.[26,27]

In conclusion, the administration of high and frequent doses of PPI–amoxicillin dual therapy may not be effective against the eradication of *H. pylori* infection, especially in our province, where clarithromycin resistance is prevalent.

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