Biomedical Sciences and Clinical Medicine. 2022;61(2):60-5.
doi: 10.12982/CMUMEDJ.2022.09
https://www.med.cmu.ac.th/bscm/

BSCM
Biomedical Sciences and Clinical Medicine

Original Article **Open Access**

High-dose Proton Pump Inhibitor Versus Standard-dose Proton Pump Inhibitor in PPI-based Triple Therapy for *Helicobacter pylori* Eradication in Lampang Hospital: A randomized Controlled Trial

Tharadol Poolthawee

Department of Internal Medicine, Lampang Hospital, Lampang, Thailand

Correspondence:Tharadol Poolthawee, MD, Department of Internal Medicine, Lampang Hospital, Lampang 52000, Thailand.
E-mail:Tharadol4507@gmail.com

Received: August 1, 2021;
Revised: September 6, 2021;
Accepted: September 22, 2021

ABSTRACT

OBJECTIVE The study aimed to compare the eradication rates with high-dose proton pump inhibitor (PPI) and standard-dose PPI in PPI-based triple therapy as first-line treatment for *H. pylori* eradication.

METHODS This prospective, open label, randomized controlled trial. A total of 150 patients infected with *H. pylori* diagnosed by rapid urease test were randomly assigned to one of 2 groups. The first group was treated with standard dose PPI-based triple therapy (omeprazole 20 mg bid, amoxicillin 1000 mg bid, and clarithromycin 500 mg bid) for 14 days and the second with high dose PPI-based triple therapy (omeprazole 40 mg bid, amoxicillin 1,000 mg bid, and clarithromycin 500 mg bid) also for 14 days. *H. pylori* eradication was evaluated using a urea breath test. Patient compliance and side effects were also recorded.

RESULTS In all, 75 patients were assigned each group. The *H. pylori* eradication rate in the high-dose PPI based triple therapy group was 92% by intention-to-treat (ITT) analysis and 93.05% by per-protocol (PP) analysis, compared with the standard-dose PPI based triple therapy group values of 84% and 85.92% ($p < 0.001$ and 0.032), respectively. Side effects were mild in both groups with no significant differences between groups.

CONCLUSIONS High-dose PPI based triple therapy provides a higher eradication rate of *H. pylori* infection than standard-dose PPI based triple therapy for first-line treatment with no difference in side effects.

KEYWORDS High-dose PPI based triple therapy, *Helicobacter pylori* eradication, Lampang Hospital

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a spiral-shaped, gram-negative bacterium, measuring 0.6×3.5 microns that can be passed from person to person through direct contact with saliva, vomit or fecal matter. *H. pylori* can also be spread through contaminated food or water. *H. pylori* colonizes the human stomach and is a causative agent of various gastroduodenal diseases, including gastritis, gastric ulcer, duodenal ulcer, mucosa-associated lymphoid tissue lymphoma, and gastric cancer. In 1994, *H. pylori* was categorized as a class I (definite) carcinogen by the International Agency for Research on Cancer (IARC), a division of the World Health Organization (WHO) indicating that eradication of *H. pylori* could reduce the risk of gastric cancer (1).

H. pylori infection is highly prevalent worldwide; more than half the world's population is infected (2). In Thailand, the prevalence of *H. pylori* infection is 45.9%, mostly in the north

and northeast regions of the country where the rates are 46.9% and 60.0%, respectively. The prevalence rates of *H. pylori* infection in the central and south regions of Thailand are 39% and 14.4%, respectively (3).

According to the Thai Consensus on *H. pylori* treatment 2015, the first-line regimen is standard PPI-based triple therapy including proton pump inhibitor (PPI), amoxicillin, and clarithromycin or metronidazole for 10-14 days. The reported eradication rate of *H. pylori* with this regimen was 85% (4). An alternative first-line regimen is sequential therapy including PPI and amoxicillin for the first 5 days and PPI, clarithromycin, and metronidazole for the following 5 days. The eradication rate of *H. pylori* with the sequential regimen was 90% (5,6). Another alternative first-line regimen is concomitant therapy which includes PPI, amoxicillin, clarithromycin, and metronidazole for 10 days. The eradication rate of *H. pylori* with the concomitant regimen was 96.4% (7).

The current rate of successful eradication with a clarithromycin-containing triple therapy regimen is lower than 80% in many Southeast Asian countries, including Thailand. Factors affecting the eradication rate are antibiotic resistance of *H. pylori*, variation in *CYP2C19* genotypes among individual patients, differences in drug regimens, and the degree of patient compliance (8,9). Many studies have been conducted on modifying regimens to increase efficacy of *H. pylori* eradication (10,11). In spite of those efforts, the current first-line regimens are still the standard PPI-based triple therapy, sequential therapy, and concomitant therapy. Although the sequential therapy is more effective in eradication of *H. pylori* than the standard triple therapy, the sequential therapy can be negatively affected by compliance problems, e.g., some patients were confused about following this regimen. Concomitant therapy, taking clarithromycin with metronidazole has more side effects than the standard triple therapy, so that regimen is used more often in general hospitals than the standard PPI-based triple therapy because the side effects can be more easily mitigated in a hospital setting.

This study endeavored to evaluate a potentially more effective PPI-based triple therapy with the limitation of the kinds of proton pump inhibitors and antibiotics available in a general hospital and could not being able to detect *CYP2C19* genotypes. Many studies have suggested that sustained control of intragastric pH at 6 or above increases the bactericidal efficacy of oral antibiotics (12,13). Based on the knowledge that decreasing stomach acidity increases the efficacy of antibiotics, we used a high dose proton pump inhibitor (omeprazole 80 mg/day) instead of the standard dose proton pump inhibitor (omeprazole 40 mg/day) in PPI-based triple therapy. This increase is supported by studies which have reported that high dose PPI (omeprazole 80 mg/day) has no side effects (14,15). This study did not, however, increase the dose of antibiotics known to frequently cause side effects. This study compared high dose PPI (omeprazole 80 mg/day) with standard dose PPI (omeprazole 40 mg/day) in PPI-based triple therapy in terms of *H. pylori* eradication rate and side effects.

METHODS

Study design and participants

This prospective, open labeled, randomized controlled trial study was conducted in Lampang Hospital from April to June 2021. Our protocol was approved by Lampang Hospital Ethics Committee in Human Research. This trial was retrospectively registered with the Thai Clinical Trial Registry (TCTR20210829002). Adult patients (age > 18 years) with *H. pylori* infection who had not received prior eradication therapy were eligible for enrollment. The diagnosis of *H. pylori* infection was based on positive results of the rapid urease test. Subjects with any one of the following criteria were excluded from the study: [1] history of gastric cancer or gastrectomy, [2] severe concurrent disease or malignancy, [3] pregnant or lactating, [4] alcohol abuse or drug addiction, [5] previous allergic reaction to study drugs, [6] a history of taking PPI, bismuth or antibiotics within the previous 4 weeks, and [7] subjects who declined to participate. Signed informed consent was obtained from all participants. If

subjects requested to withdraw from the study for any reason or if they had serious side effects from study drugs, e.g., anaphylaxis, hypotension, or chest discomfort, their participation in the study was terminated immediately.

Randomization and interventions

Eligible patients were randomized to receive either standard dose PPI-based triple therapy (omeprazole 20 mg bid, amoxicillin 1000 mg bid, and clarithromycin 500 mg bid) for 14 days or high dose PPI-based triple therapy (omeprazole 40 mg bid, amoxicillin 1,000 mg bid, and clarithromycin 500 mg bid) for 14 days. Randomization was performed in blocks of four using computer generation and the process was concealed from investigators until the interventions were assigned. Patients were instructed to adhere to the drug regimen and were advised of the possible side effects. Baseline characteristics (gender, age, underlying diseases, and endoscopic findings) were recorded. Eradication rate was assessed six weeks after completion of the course of therapy by performing the urea breath test (UBT). Successful eradication was defined as negative UBT. Compliance and side effects were evaluated by self-reporting and direct interviews at the end of the treatment. Good drug compliance was defined as drug consumption > 80% of the total dosage.

Outcomes

The primary end point of the study was the eradication rate, which was assessed by intention-to-treat (ITT) and per-protocol (PP) analyses. All randomized patients were included in the ITT analysis. Patients who did not return for the follow up urea breath test were considered treatment failures. Patients who failed to take at least 80% of their prescribed drugs or were lost to follow up were excluded from the PP analysis. The secondary endpoints were side effects of the study drugs.

Statistical analysis

To calculate the sample size, we hypothesized that the eradication rate of the standard dose PPI-based triple therapy was 80% and that the high dose PPI-based triple therapy would achieve a 95% eradication rate (a 15% difference). Our sample size estimate was 75 individuals for each group (a total of 150), given a power of 80% and a confidence level of 95%.

Statistical differences in eradication rates among the different regimens were assessed using the chi-square test. Demographic data and frequencies of adverse reactions were compared using chi-square test or Fisher's exact test as appropriate. $P < 0.05$ were considered to be statistically significant. The statistical analyses were performed using Stata/SE 10.1.

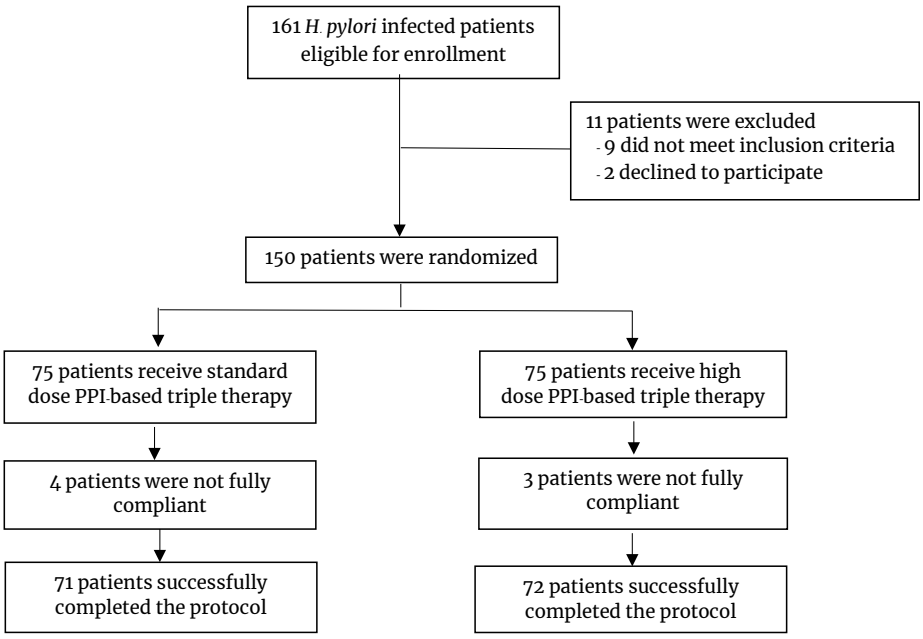

Figure 1. Flow chart of patients during the study

RESULTS

Baseline characteristics of patients

From April to June 2021, 161 patients with *H. pylori* infection from Lampang Hospital were evaluated. Of those patients, 150 were enrolled and randomized to receive one of two regimens. Seventy-five patients were assigned to receive standard dose PPI-based triple therapy and 75 patients received high dose PPI-based triple therapy. The flow chart of patients included in the study is displayed in Figure 1. Baseline characteristics of patients in the two treatment groups are summarized in Table 1. No differences were observed between the two groups in terms of baseline characteristics of patients. Most of patients were female (58.7% in the standard-dose PPI group and 61.3% in the high-dose PPI group). The most frequent endoscopic finding was gastritis (84% in the standard-dose PPI group and 82.67% in the high-dose PPI group). All patients received follow-up treatment. Almost all patients showed good compliance (94.67% in the standard-dose PPI group and 96% in the high-dose PPI group).

Eradication rates of *H. pylori* infection

The eradication rates by intention-to-treat (ITT) and per-protocol (PP) analysis are shown in Table 2. In the standard dose PPI-based triple therapy group, ITT and PP analyses of the eradication rates were 84% and 85.92 %, respectively;the eradication rates in the high dose PPI-based triple therapy group were 92% by ITT analysis and 93.05% by PP analysis. The eradication rates were higher in the high-dose PPI group than in the standard-dose PPI group by both ITT analysis and PP analysis ($p < 0.001$ and 0.032, respectively).

Side effects of the study drugs

Side effects, including bitter taste, diarrhea, nausea, headache, and dizziness were all mild and did not significantly differ between the two groups (Table 3). Bitter taste was the most commonly reported side effect in both groups (68% in the standard-dose PPI group vs. 72% in the high-dose PPI group; $p = 0.722$).

DISCUSSION

The results of this study showed the efficacy of the *H. pylori* eradication of high dose-PPI based triple therapy was higher than that of the standard dose-PPI based triple therapy with no difference in side effects. Advantages of the high dose regimen include that it is available in general hospitals, patients reported

Table 1. Baseline characteristics of subjects in the two treatment groups

	Standard dose PPI-based triple therapy	High dose PPI-based triple therapy	*p*-value
Male gender, n (%)	31 (41.3)	29 (38.7)	0.868
Age, mean	54.51 ± 14.94	53.88 ± 14.63	0.796
Underlying disease			
- DM, n (%)	8 (10.67)	13 (17.33)	0.347
- HT, n (%)	19 (25.33)	28 (37.33)	0.159
- DLP, n (%)	13 (17.33)	15 (20.00)	0.834
- IHD, n (%)	4 (5.33)	2 (2.67)	0.681
- Old CVA, n (%)	5 (6.67)	2 (2.67)	0.442
- CKD, n (%)	2 (2.67)	1 (1.33)	1.000
- Cirrhosis, n (%)	7 (9.33)	2 (2.67)	0.166
Endoscopic finding			
- Gastritis, n (%)	63 (84.00)	62 (82.67)	
- Duodenitis, n (%)	0 (0)	1 (1.33)	0.731
- Gastric ulcer, n (%)	10 (13.33)	8 (10.67)	
- Duodenal ulcer, n (%)	2 (2.67)	4 (5.33)	
Good compliance, n (%)	71 (94.67)	72 (96.00)	1.000
Follow-up, n (%)	75 (100.00)	75 (100.00)	1.000

Table 2. Efficacy of standard dose and high dose PPI-based triple therapy for *Helicobacter pylori* eradication

	Standard dose PPI-based triple therapy	High dose PPI-based triple therapy	*p*-value
Intention to treat (ITT)	63/75 (84.00)	69/75 (92.00)	<0.001
Per protocol (PP)	61/71 (85.92)	67/72 (93.05)	0.032

Table 3. Side effects of standard dose and high dose PPI-based triple therapy

	Standard dose PPI-based triple therapy	High dose PPI-based triple therapy	*p*-value
Bitter taste, n (%)	51 (68.00)	54 (72.00)	0.722
Diarrhea, n (%)	3 (4.00)	4 (5.33)	1.000
Nausea, n (%)	10 (13.33)	8 (10.67)	0.802
Headache, n (%)	2 (2.67)	3 (4.00)	1.000
Dizziness, n (%)	3 (4.00)	3 (4.00)	1.000
Skin rash, n (%)	0 (0.00)	0 (0.00)	-

ease in taking medication as prescribed and only mild side effects. Previous studies have suggested that sustained control of intragastric pH at 6 or above increases the bactericidal efficacy of oral antibiotics (12,13). We assumed that high dose PPI could reduce acidity in the stomach and thus increase bactericidal efficacy of the antibiotics. The current rate of *H. pylori* eradication using a clarithromycin-containing triple therapy regimen is lower than 80% in many studies, but our study found that the *H. pylori* eradication rate of standard-dose PPI based triple therapy was 84%. That difference may have resulted from the low prevalence of clarithromycin resistance among our patients (8,9).

The results of this study showed the eradication rate of *H. pylori* with high-dose PPI based triple therapy was 92% and more than 84% for standard-dose PPI based triple therapy. We could not directly compare the eradication rates of *H. pylori* observed in this study with sequential therapy and concomitant therapy reported in other studies (5-7). The advantages of standard triple therapy include being more efficacious than sequential therapy, that patients find taking the concomitant therapy medication to be easier and that there is a lower risk of side effects than with multiple antibiotics.

We found only mild side effects of the study drugs, including bitter taste, diarrhea, nausea, headache, and dizziness. The most common side effect was bitter taste, which most likely stemmed from clarithromycin. In the standard treatment, we used high dose PPI in some patients such those with Zollinger-Ellison syndrome. Some studies have reported that high dose PPI (omeprazole 80 mg/day) produced no side effects (14,15), indicating that high dose PPI can be used safely.

Strengths of this study included being a randomized controlled trial and that it was conducted in a general hospital following ordinary practices. A limitation of this study is that we did not test *CYP2C19* genotypes and clarithromycin resistance which constitute the main causes of failure to eradicate *H. pylori*. Because we studied subjects in the same hospital, we assumed that no significant difference in *CYP2C19* genotypes and clarithromycin resistance existed between the two groups. The fact of studying in a single hospital constituted a limitation, as well, because of restricted diversity of *CYP2C19* genotypes and clarithromycin resistance. Another limitation is that we did not monitor the intragastric pH of our subjects. We assumed that an open-label design for our study would not affect the results because we checked the compliance of all subjects and assessed eradication rates by performing the standard urea breath test. Further studies are recommended to test for the effect of different *CYP2C19* genotypes and to explore the prevalence of clarithromycin resistance.

In conclusion, high-dose PPI based triple therapy achieves a higher eradication rate of *H.*

pylori infection than standard-dose PPI based triple therapy for first-line treatment with no difference in side effects.

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