Original Article

7-Day High-Dose Proton Pump Inhibitor versus 10-day Standard Concomitant Therapy for *Helicobacter pylori* Eradication in Thai Patients: A Randomized Controlled Trial

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Background: A 10-day standard concomitant therapy (SCT) is a first-line *Helicobacter pylori* treatment option with slightly higher eradication rates as compared to a standard triple therapy. More aggressive acid suppression by high-dose proton pump inhibitor (PPI) may allow shortening treatment duration without compromising eradication rates. This study was aimed to compare the *H. pylori* eradication rates between a 7-day high-dose PPI (modified) concomitant therapy (MCT) and a 10-day standard concomitant therapy (SCT).

Materials and Methods: This open label, randomized study was conducted at Rajavithi Hospital, Bangkok, Thailand between November 2016 and November 2017. Patients with active *H. pylori* infection (n = 240) were included and randomized (1: 1) into either 7-day MCT (omeprazole 40 mg bid., amoxicillin 1,000 mg bid., clarithromycin 500 mg bid. and metronidazole 400 mg tid. for 7 days) or 10-day SCT (omeprazole 20 mg bid., amoxicillin 1,000 mg bid., clarithromycin 500 mg b.i.d. and metronidazole 400 mg t.i.d. for 10 days). *H. pylori* eradication was evaluated by ^{14}C-urea breath test at 4-6 weeks after the completion of treatment.

Results: A total of 120 patients were randomized into each treatment group. In intention-to-treat analysis, *H. pylori* eradication rate was 88.3% (106/120) and 88.3% (106/120) in the 7-day MCT and 10-day SCT groups, respectively (p>0.99). In per-protocol analysis, *H. pylori* eradication rate was 94.6% (106/112) and 95.5% (106/111) in the 7-day MCT and 10-day SCT groups, respectively (p = 0.769). Treatment-related adverse events were mostly mild and well tolerated, which occurred in a similar frequency in both groups.

Conclusion: 7-day MCT was safe and able to achieve similar eradication rate as compared with a 10-day SCT. This novel shorter MCT may be a practical alternative first-line treatment option for *H. pylori* eradication in Thailand since shorter treatment is associated with lesser cost and better tolerability.

Keywords: Concomitant therapy, *Helicobacter pylori*, Eradication, Thailand

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Helicobacter pylori infects up to 40% of the adult population in Asia and is associated with a wide range of upper gastrointestinal diseases including gastritis, peptic ulcer disease, mucosa associated lymphoid tissue lymphoma and gastric cancer[1]. Recently, eradication rates of *H. pylori* infection with a 14-day standard triple therapy has globally declined, mainly due to the increasing prevalence of clarithromycin-resistance strains. Notably, the expected eradication rates by standard triple therapy in Thailand are currently 80 to 85%. As a result, standard triple therapy is no longer recommended as an empiric first-line therapy in many countries with high prevalence of clarithromycin-resistance *H. pylori* strains, thus, better regimens that provide reliably high eradication rates with low side effects are required[2,3].

The success of eradication regimens depends on many factors including compliance, antibiotic resistance, and adequate acid suppression[3,4]. A survey of 5 teaching hospitals revealed that the clarithromycin resistance rate in Thailand varied from 5 to 29% (median 14%) and metronidazole rate ranged from 30 to 52%[5]. Proton pump inhibitors (PPI) are metabolized by cytochrome P450 enzymes in the liver, and their efficacies are largely depending on the expression/activity of CYP2C19 in each individual (CYP2C19 genotypes)[6]. Extensive CYP2C19 metabolizers have more rapid PPI clearance than the intermediate metabolizer and poor metabolizer, which thereby may have decreased acid inhibition effects of PPI, especially omeprazole (mainly metabolized by CYP2C19). Notably, the effect of CYP2C19 genotypes on PPI efficacy may overcome by increasing the dose and/or frequency of PPI administration[7]. A study of Thai people revealed that the prevalence of CYP2C19 extensive metabolizer was 56%, intermediate metabolizer was 30%

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and poor metabolizer was 14%[8]. In addition, it has been suggested that more potent acid suppression by double-dose PPI or vonoprazan (a potassium-competitive acid blocker) may allow shortening duration of *H. pylori* treatment and may even overcome clarithromycin resistance.

Concomitant therapy, a 4-drug regimen containing 3 antibiotics (clarithromycin, amoxicillin and metronidazole) with a PPI for a duration of 3 to 10 days, has proven successful in the presence of moderate clarithromycin resistance[9]. Several randomized controlled trials have demonstrated that concomitant therapy is more effective than and is equally well tolerated as standard triple therapy[10]. A meta-analysis of 15 studies (1723 patients) revealed a mean *H. pylori* eradication rate of 90% for concomitant therapy. A tendency towards better results with longer treatment duration (7 to 10 days vs. 3 to 5 days) has been observed, so it seems reasonable to recommend the length of treatment by achieving maximal eradication rates (10 days). Thus, the success rates among different PPI used were similar[11]. Nevertheless, despite their slightly higher eradication rates as compared to standard triple therapy, concomitant therapies have been associated more frequent side effects, particularly with longer duration of treatment.

According to the Thailand guidelines for the management of dyspepsia and *Helicobacter pylori* issued in 2015 suggested that either 10 days of sequential therapy and 10 days of concomitant therapy are the alternative treatment options for first-line *H. pylori* eradication in Thailand[12]. Both regimens have shown to achieve >90 to 95% eradication rates which are higher than that of 10 to 14 days of triple therapy (80 to 85%)[13,14].

Taken together, we speculate that the efficacy of concomitant therapy can be further improved by increasing the dose of PPI which may allow shortening the duration of treatment. Therefore, this study aimed to evaluate the efficacy of the 7-day modified concomitant therapy (MCT), by doubling the dose of omeprazole, compared to a 10-day standard concomitant therapy (SCT).

Materials and Methods

Study design and participants

This was a single center, open label, randomized controlled study conducted in Rajavithi hospital, Bangkok, Thailand between November 2016 and November 2017. Entry criteria included adult patients (age 18 to 65 years old) with active *H. pylori* infection diagnosed endoscopically. During endoscopy, 4 biopsy samples from 4 different sites (2 from antrum and 2 from body) were obtained for rapid urease test (≥2 pieces) and histological examination ((≥2 pieces). The presence of *H. pylori* was defined as positivity of rapid urease test and/or positivity of *H. pylori* on histology. Exclusion criteria included patients with (1) allergy to study drugs; (2) previous eradication for *H. pylori*; (3) use of bismuth containing drugs or antibiotics within 4 weeks; (4) history of gastric cancer or gastrectomy; (5) severe comorbidity e.g. end-stage renal disease, advanced cirrhosis, congestive heart failure, severe chronic obstructive pulmonary disease and active cancers; (6) pregnant or lactating women; and (7) alcohol abuse or drug addiction.

Randomization and treatment regimens

Eligible subjects were randomized using a block randomization 1: 1 in 20 person per each group and list to one of the two regimen: either a 7-day MCT (omeprazole 40 mg bid., amoxicillin 1,000 mg bid., clarithromycin 500 mg b.i.d. and metronidazole 400 mg tid.) or a 10-day SCT (omeprazole 20 mg bid., amoxicillin 1,000 mg bid., clarithromycin 500 mg bid. and metronidazole 400 mg tid.) in which the process was concealed to investigators until interventions were assigned. The protocol of this research was reviewed and approved by the Ethics Committee of Rajavithi Hospital. Written informed consents were obtained from all patients prior to enrollment. Patients were instructed to adhere to the drug regimen and were advised of the possible side effects. Compliance and side effects were evaluated by self-reporting and direct interview at the end of treatment. A good drug compliance was defined as drug consumption >90% of the total dosage. Eradication rate was assessed by performing ^{14}C-urea breath test (UBT) at 4 to 6 weeks after completion of therapy. Successful eradication was defined as negative UBT. If the subjects have indication to repeat endoscopy, a subject was regarded as post-treatment *H. pylori* negative when the final follow-up examination did not reveal bacteria in any of three methodologies (rapid urease test, histology and UBT).

The primary end point of the study was the *H. pylori* eradication rate assessed by intention-to-treat (ITT) and per-protocol (PP) analyses. All randomized patients were included in the ITT analysis. Patients who failed to take at least 90 % of their prescribed drugs or who lost to follow-up were excluded from the PP analysis. The secondary end points were the prevalence of adverse reactions. Side effects of treatment were assessed by personal interview using questionnaires for each patient. The potential adverse reactions listed in the questionnaires were bitter taste, nausea and vomiting, diarrhea, and fatigue. New symptoms and exacerbation of pre-existing symptoms during the period of treatment were determined to be treatment-related adverse reactions. Major adverse reactions were defined as symptoms that significantly disturbed patient's daily life.

Statistical analysis

For the sample size calculation, we hypothesized that there would be approximately 11% difference in the eradication rates between the two regimens. Knowing that the eradiation rate of 10-day SCT was approximately 96%, our sample size estimation was 120 for each group, given a power of 80% and a confidence level of 95%, assuming a 10% loss to follow-up. Statistical differences in eradication rates among the different regimen were assessed by Chi-square test. The demographic data and frequencies of adverse events were compared using Chi-square test or Fisher's exact test, as appropriate. The *p*-values <0.05 were considered

to be statistically significant. The statistical analyses were performed using the Stata/SE 10.1

Results

Baseline characteristics

A total of 351 patients with active *H. pylori* infection were evaluated and 240 patients were included in this study and randomized in to one of two regimens. The flow of patients through the study is displayed in Figure 1. Baseline demographic data are shown in Table 1. Patients in the 7-day MCT group were older, have more cardiovascular comorbidity and more endoscopic finding as erosive gastritis than those in the 10-day SCT group.

Eradication rate of treatment regimens

The eradication rates by PP and ITT analysis are shown in Table 2. In the 7-day MCT group, ITT and PP analyses of the eradication rates were 88.3% and 94.6%, respectively, whereas the eradication rates in the 10-day SCT group were 88.3% by ITT analysis and 95.5% by PP analysis. These eradication rates are not significantly different between the two groups.

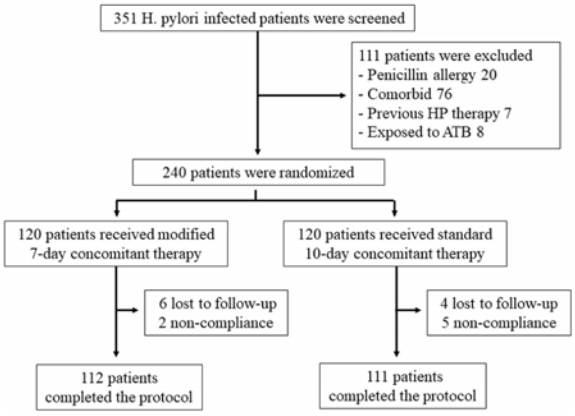

Figure 1. Flow chart of patients during the study.

Side effects and compliance with therapy

Documented adverse reactions were shown in Table 3. The common side effects included bitter taste, nausea/vomiting, abdominal pain, diarrhea, headache, and fatigue which were mostly mild and relatively well-tolerated without the need of treatment modification. Bitter taste was the most commonly reported adverse effect in both groups (72.3% in the 7-day MCT group vs. 66.7% in the 10-day SCT group; $p = 0.36$). Eight patients experienced major adverse event from bitter taste (5 patients in in the 7-day MCT group and 3 patients in 10-day SCT group). Headache and diarrhea were more frequently reported in 10-day SCT group more than 7-day MCT group ($p = 0.05$). Other side effects were not significant difference between 2 groups.

Six patients in the 7-day MCT group and 4 patients in the 10-day SCT group were lost to follow-up. Drug compliance with the 7-day MCT regimen was 112/120 (93.3%) and 111/120 (92.5%) in the 10-day SCT group which were not significant different between groups.

Discussion

Recent data revealed that *H. pylori* eradication rate with triple therapy regimen including PPI, amoxicillin and clarithromycin in many regions has declined to 80% or below[15,16]. When the prevalence and pattern of antibiotic resistance are unknown, it is suggested that only regimens that are expected to provide eradication rate at least 90% should be prescribed as empiric therapy[17]. Treatment success with eradication rate greater than 90% by intention-to-treat analysis has been defined as "good" and ≥95% as "excellent" outcome[15]. Important factors affecting the

Table 1. Baseline characteristics of subjects in both treatment groups

	7-day MCT (n = 120)	10-day SCT (n = 120)	*p*-value
Male gender, n (%)	50 (41.7)	64 (53.3)	0.070
Age (years), mean (SD)	56.9 (14.4)	50.7 (12.6)	<0.001
Body mass index (kg/m^2), mean (SD)	24.3 (3.7)	24.6 (4.7)	0.535
Smoking, n (%)	16 (13.3)	18 (15)	0.711
Alcohol, n (%)	16 (13.3)	23 (19.2)	0.221
Cardiovascular disease, n (%)	21 (17.5)	8 (6.7)	0.010
Diabetes mellitus, n (%)	25 (20.8)	24 (20)	0.873
Hypertension, n (%)	40 (33.3)	34 (28.3)	0.402
Dyslipidemia, n (%)	34 (28.3)	22 (18.3)	0.067
Cirrhosis, n (%)	36 (30)	47 (39.2)	0.135
Erosive gastritis, n (%)	57 (47.5)	40 (33.3)	0.025
Hemorrhagic gastritis, n (%)	26 (21.7)	23 (19.2)	0.631
Atrophic gastritis, n (%)	23 (19.2)	32 (26.7)	0.167
Gastric ulcer, n (%)	21 (17.5)	24 (20)	0.620
Duodenal ulcer, n (%)	5 (4.2)	9 (7.5)	0.271

MCT = modified concomitant therapy, SCT = standard concomitant therapy

Table 2. Efficacy of modified 7-day concomitant therapy (7-day MCT) with standard 10-day concomitant therapy (10-day SCT)

	7-day MCT (n = 120)	10-day SCT (n = 120)	*p*-value
Intention-to-treat	106/120 (88.3)	106/120 (88.3)	0.99
Per-protocol	106/112 (94.6)	106/111 (95.5)	0.77

Data are expressed as n (%)

Table 3. Side effects of modified 7-day concomitant therapy with standard 10-day concomitant therapy

	7-day MCT (n = 120)	10-day SCT (n = 120)	*p*-value
Nausea/vomiting	34 (30.4)	32 (28.8)	0.803
Bitter taste	81 (72.3)	74 (66.7)	0.359
Headache	11 (9.8)	21 (18.9)	0.050
Dizziness	24 (21.4)	25 (22.5)	0.844
Diarrhea	19 (17)	31 (27.9)	0.050
Fatigue	21 (18.8)	18 (16.2)	0.618

Data are expressed as n (%)

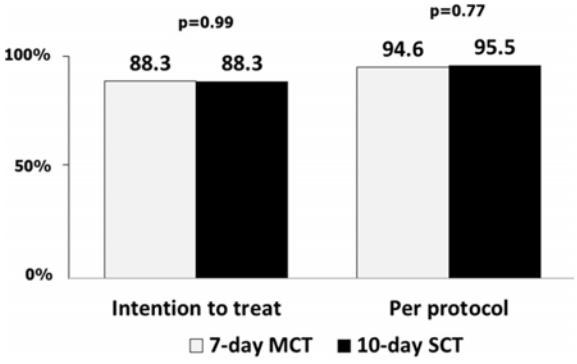

Figure 2. Efficacy of 7-day modified concomitant therapy versus 10-day standard concomitant therapy.

eradication rate are antibiotic resistance, CYP2C19 genotypes, drug regimen and patient compliance. The regimen that can optimize these factors might be a candidate for ideal empiric therapy[18].

Antibiotic resistance is the major cause of treatment failure for *H. pylori*, and reliable information on the prevalence of antibiotic resistance is crucial for choosing the best treatment regimen for a region or for a patient[19]. From a microbiological standpoint, the most rational way to overcome antibiotic resistance would be the use of a combination of drugs for which resistance does not appear to be a problem, so clarithromycin-based regimens should not be recommended in geographical areas with high clarithromycin resistance rates (>15%)[9]. In this context, concomitant therapy (non-bismuth-based quadruple therapy) seems to be an attractive alternative empiric treatment, however the duration of therapy is still debatable[11].

In a pilot study to identify the optimal duration of concomitant therapy (rabeprazole 20 mg bid., amoxicillin 1,000 mg bid., metronidazole 400 mg tid., and clarithromycin MR 1 g once daily) in Thai subjects with non-ulcer dyspepsia, 5-day regimen was inferior to 10-day concomitant therapy (eradication rates: 89% vs. 96%, respectively)[14]. In addition, 5-day concomitant therapy has also shown its failure in studies from Latin America and South Korea[20,21]. However, in the present study, 7-day MCT achieved an acceptable efficacy (88% by ITT and 95% by PP analysis) which were not significant different to that of 10-day SCT (88% by ITT analysis and 96% by PP analysis). This finding is somewhat similar to the prospective study from Japan evaluating 1-week concomitant therapy consisting of omeprazole, amoxycillin, metronidazole and roxithromycin. Successful eradication was documented in 92% of patients by ITT analysis, and in 95% of patients by PP analysis[22].

Higher incidence and severity of treatment-related side effects, particularly from the use of metronidazole, has been the major concern of concomitant therapy. In a meta-analysis by Essa et al (6 studies included 846 patients), there was no serious side effects were reported in any of the studies, apart from anaphylactic reactions to medication, however mild-to-moderate side effects were common in 27 to 51% of patients treated with the concomitant regimen[23]. Similarly, in the present study, treatment-related adverse events were very common, especially bitter taste (presence in up to 70% of patients). Most side effects were mild and well-tolerated which tended to be more common in the 10-day SCT group. It should be noted that there were several differences regarding the trial design of this study from the previous study of concomitant therapy in Thailand which may partly explain a conflicting result[14]. Firstly, the present study conducted in *H. pylori* positive patients with various gastrointestinal conditions other than functional dyspepsia. Secondly, we

used omeprazole as the sole PPI in this study. Since omeprazole is the most available and is the recommended first-line PPI for most situations in Thailand, the present study may be a better representative of majority of cases in real-world practice in Thailand. Thirdly, the antibiotics used in this study were all generics. Fourthly, we doubled the dose of omeprazole as we hypothesized that increased acid suppression may allow shortening duration, particularly for those patients who were CYP2C19 extensive metabolizers. Furthermore, *H. pylori* is able to survive in a pH range between 4 and 5, however it hardly proliferates and reduces the efficacy of the growth-dependent antibiotics such as amoxicillin, clarithromycin and tetracycline. More potent and sustain acid inhibition by double-dose omeprazole may drive *H. pylori* to its maximal proliferative phase (gastric pH 6 to 7) which theoretically increases susceptibility of *H. pylori* to growth-dependent antibiotics[24].

Poor adherence is one of the major reasons for failure of *H. pylori* eradication after antibiotic resistance. About 10% of patients on triple therapy are estimated to fail to take at least 60% of their medications[25], a threshold at which significantly lower rates of eradication have been proven. In this study, drug compliance was good (>90% in both groups) possibly because the shorter duration and less complex regimen when compared other standard regimens, such as 14-day triple therapy, 10-day sequential therapy and 10-day concomitant therapy. It is known that patients who are enrolled in clinical trials tend to be more motivated and more cooperative with physician's instruction than those treated outside clinical trial which, as a result, may be associated with better drug compliance and clinical outcomes. Taken this into real-life, we believe that careful explanations about the importance of treatment, regimen details, anticipated side-effects and their self-management, will enhance drug compliance, and produce higher rates of successful eradication with concomitant therapy.

There are several limitations in this study. Firstly, we did not evaluate the prevalence of antimicrobial resistance and CYP2C19 genotypes so we did not know the exact reason for treatment failure and also the prevalence of antimicrobial resistance in our study population. Notably, previous study from our hospital reported that the prevalence of *H. pylori* resistance to clarithromycin, amoxicillin, and metronidazole were 14%, 21%, and 55%, respectively[26]. Secondly, this study conducted in a single referral center study in which most subjects were from Bangkok and the Central Region of Thailand. Since antibiotic resistant pattern of *H. pylori* varies among different medical care settings and geographical regions so the result of this study may not represent the whole country. Lastly, there is a possibility for bias as this is an open label study. Nevertheless, we minimized any potential bias by randomization and objective measurement of primary outcome.

Conclusion

The 7-day MCT (double-dose PPI) achieved acceptable treatment success which was comparable to that of a 10-day SCT for *H. pylori* eradication. Although side effects are common, both concomitant regimens are safe and well-tolerated. This 7-day MCT may be a practical alternative, first-line treatment option for *H. pylori* eradication in Thailand since shorter treatment is associated with less cost and better tolerability.

What is already known on this topic?

A 10-day concomitant therapy is recommended as one of the first-line *H. pylori* treatment options in Thailand with higher eradication rates, but also higher rates of treatment-related side effects, as compared with a 14-day standard triple therapy.

What this study adds?

A 7-day modified (double-dose omeprazole) concomitant therapy achieved similar eradication rates as compared with a 10-day concomitant therapy. This novel shorter concomitant regimen may be a practical alternative first-line treatment option for *H. pylori* eradication in Thailand.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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