

RESEARCH ARTICLE

Outcomes of a Randomized Controlled Trial Comparing Modified High Dose Omeprazole and Amoxicillin Triple Therapy with Standard Triple Therapy for *Helicobacter Pylori* Eradication

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Abstract

Background: *Helicobacter pylori* (*H. pylori*) infection is related to peptic ulcer diseases and gastric cancer and eradication of *H. pylori* should be expected to decrease the risk of their development. Factors affecting *H. pylori* eradication are antibiotic resistance, *CYP2C19* genotypes, drug regimen and patient compliance. Increment of omeprazole and amoxicillin dosage in clarithromycin-containing triple therapy regimen may overcome these problems and may be a better choice than the conventional clarithromycin-containing triple therapy regimen. **Objective:** To compare the eradication rates with modified triple therapy (MTT) and standard triple therapy (STT) as first-line treatment. **Materials and Methods:** The study was an open label, multicenter, randomized controlled trial. A total of 170 patients infected with *H. pylori* diagnosed by rapid urease test were randomly assigned into 2 groups. The first was treated with a 14-day MTT (20 mg omeprazole t.i.d., 500 mg amoxicillin t.i.d., and 500 mg clarithromycin b.i.d.) and the second with a 14-day STT (20 mg omeprazole b.i.d., 1000 mg amoxicillin b.i.d., and 500 mg clarithromycin b.i.d.). *H. pylori* eradication was evaluated by ¹⁴C-urea breath test. *CYP2C19* genotypes, clarithromycin resistance, side effects and patient compliance were also recorded. **Results:** There were 85 patients in each group. The *H. pylori* eradication rate in the MTT group was 84.7% by ITT analysis and 91.1% by PP analysis, compared to the STT group values of 76.5% and 87.8% ($p = 0.18$ and 0.51), respectively. *CYP2C19* genotypes and patient compliance were similar in both groups. Prevalence of clarithromycin resistance was 7.0%. Side effects were all mild with no significant differences between the two groups. **Conclusions:** MTT is not superior to STT. From this study, MTT may not be recommended as the first-line treatment for *H. pylori* infection in Thailand because eradication rates proved to be less than 90% by ITT analysis.

Keywords: Modified high dose- omeprazole- amoxicillin- triple therapy- *Helicobacter pylori* eradication- Thailand

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Introduction

H. pylori infection is related to peptic ulcer diseases and gastric cancer (Marshall et al, 1995; Correa et al, 1992). *H. pylori* infection is highly prevalent worldwide. More than half of the world's population suffers from this infection (Everhart, 2000). For example, the prevalence of *H. pylori* infection in the northeast region of Thailand is 67.1%. The premalignant histological change of gastric cancer (e.g. atrophic change and intestinal metaplasia) was also highly prevalent in this region with the rate of 59.5% (Atisook et al, 2003). According to previous studies, the best way to prevent gastric cancer development is to

eradicate *H. pylori* infection (Ford et al, 2014; Fuccio et al, 2009).

The current rate of successful eradication with a clarithromycin-containing triple therapy regimen is lower than 80% in many Southeast Asian countries, including Thailand (Ang et al, 2015; Graham and Fischbach, 2010; Jianjaroonwong, 2013; Yoon et al, 2013). Factors affecting the eradication rate are antibiotic resistance of *H. pylori*, *CYP2C19* genotypes in individual patients, drug regimen, and patient compliance. Clarithromycin and metronidazole resistance is increasing steadily and leads to triple therapy regimen ineffectiveness. Several studies in Thailand reported clarithromycin resistant rate from 3.7%

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to 29.2% and metronidazole resistant rate from 30.0% to 51.9% (Wongkusoltham et al, 2001; Mahachai et al, 2006; Tanuma et al, 2009; Vilaichone et al, 2011; Vilaichone et al, 2013). However, the most recent data from nationwide study in 2012 showed that clarithromycin resistant rate in northeast region of Thailand was only 2.1% (Vilaichone et al, 2013). Proton pump inhibitor (PPI) responsiveness depends on the expression of *CYP2C19* enzyme in each individual (*CYP2C19* genotypes). Tassaneeyakul et al predicted the majority of Thai northeast population (46.73%) as extensive metabolizer (EM) of *CYP2C19*. Based on Tassaneeyakul et al., (2002), EM patients have more rapid PPI clearance than the intermediate metabolizer (IM) and poor metabolizer (PM). Thus, acid inhibition is insufficient to accommodate antibiotic killing effect of *H. pylori* in the extensive metabolizers. The use of triple therapy regimen, including PPI, amoxicillin, and clarithromycin may be the first choice in the Northeast region, where the prevalence of clarithromycin resistance is low. Modification of triple therapy by increasing the dosage of omeprazole may overcome the insufficient acid suppression for *H. pylori* eradication among the extensive metabolizer patients.

Many studies have found that increasing the dose of omeprazole to 20 mg 3-4 times a day or increasing the frequency of amoxicillin to 3-4 times a day is more effective in the eradication of *H. pylori* with similar side effect as compared to standard dose of omeprazole or amoxicillin. No studies explored the combination of omeprazole and amoxicillin given three times a day together with clarithromycin which may be an alternative regimen to replace the conventional triple therapy regimen (Rokkas et al, 1995; Miehlke et al, 2003; Kim et al, 2008; Furuta et al, 2014). Omeprazole increment may help in cases whose *CYP2C19* expression are extensive metabolizer. Amoxicillin administration using a regimen of three to four times daily is theoretically appropriate because its antibacterial effect depends on the time above the MIC and not the AUC or Cmax (Sugimoto et al, 2014). This study compared the modified triple therapy (omeprazole 20 mg tid, amoxicillin 500 mg tid, and clarithromycin 500 mg bid) with the standard triple therapy (omeprazole 20 mg bid, amoxicillin 1,000 mg bid and clarithromycin 500 mg bid) in terms of eradication rate. The prevalence of each *CYP2C19* genotypes and the prevalence of clarithromycin-resistant *H. pylori* strains, may in part explain the high or low eradication rate among the studied patients. The result of this study may help making decision whether MTT regimen can be recommended as the first choice for *H. pylori* treatment among northeast Thai population.

Materials and Methods

Study design and participants

This was a prospective, open label, multicenter randomized controlled trial conducted in three hospitals in the northeast of Thailand (Srinagarind university hospital, Nongkhai, and Chaiyaphum provincial hospitals), from April to November 2015. Our protocol was approved by the office of the Khon Kaen university ethics committee in

human research. The Thai Clinical Trials Registry (TCTR) registration identifier was TCTR20150910001. Adult patients (age \geq 18 years old) with *H. pylori* infection who did not receive prior eradication therapy were eligible for the enrolment. The diagnosis of *H. pylori* infection was based on positivity to 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 women, (4) alcohol abuse or drug addiction, (5) previous allergic reaction to study drugs, and (6) use of PPI, bismuth containing drugs or antibiotics within 4 weeks.

Randomization and interventions

Eligible patients at each considered hospitals were randomized to receive either modified triple therapy (MTT; omeprazole 20 mg tid, amoxicillin 500 mg tid, and clarithromycin 500 mg bid) or standard triple therapy (STT; omeprazole 20 mg bid, amoxicillin 1000 mg bid and clarithromycin 500 mg bid) for 14 days. Randomization was performed in blocks of four by computer generation and the process was concealed to investigators until interventions were assigned. Signed informed consent was obtained to participate in this study. Patients were instructed to adhere to the drug regimen and were advised of the possible side effects. Eradication rate was assessed at 4 - 6 weeks after completion of therapy by performing ^{14}C -urea breath test (UBT). Successful eradication was defined as negative UBT. Compliance and side effects were evaluated by self-reporting and direct interview at the end of the treatment. A good drug compliance was defined as drug consumption $>$ 85% of the total dosage.

^{14}C -Urea Breath Test

After six hours of fasting, one capsule of ^{14}C -urea (Endo Supply Company Limited, Bangkok, Thailand) was administered orally. The breath sample was obtained 15 minutes later. The cutoff value was 45 (Negative result was defined as less than 45). Sensitivity and specificity of this test were over 95%.

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 of ^{14}C -UBT were considered treatment failures. Patients who failed to take at least 85 % of their prescribed drugs or who lost to follow up were excluded from the PP analysis.

The secondary end points were the prevalence of *CYP2C19* genotypes in patients with *H. pylori* infection and the prevalence of clarithromycin-resistant *H. pylori* strains. Blood samples were collected from the patients before eradication therapy. The *CYP2C19* genotyping for wild-type allele (*1) and three mutated alleles (*2, *3 and *17) were conducted by real-time PCR technique (Tassaneeyakul et al, 2002). The patients were categorized into three groups based on the *CYP2C19* genotype, EM (*1/*1 or *1/*17), IM (*1/*2, *1/*3, *2/*17 or *3/*17), and PM (*2/*2, *2/*3, or *3/*3).

To evaluate clarithromycin resistance, because the A-to-G transition at position 2143 (A2143G) and 2142 (A2142G) in 23S rRNA were proposed as the major mechanism, two biopsy samples from gastric antrum and body were obtained for measurement of point mutations of 23S rRNA gene of *H. pylori* at the positions of 2142 and 2143 by PCR-RFLP (restriction fragment length polymorphism) technique. When 23S rRNA gene at the position of 2142 or 2143 was wild type, patients were diagnosed to be infected with clarithromycin-sensitive strains. When 23S rRNA gene was mutated (A2142G A/G, A2142G G/G, A2143G A/G or A2143G G/G), patients were diagnosed to be infected with clarithromycin-resistant strains (Versalovic et al, 1997; Wang and Taylor, 1998; Ménard et al, 2002).

Statistical analysis

For the sample size calculation, we hypothesized that there would be approximately 18% difference in the eradication rates between the two regimens. Knowing that the eradication rate of STT was approximately 72%, our sample size estimation was 85 for each group, given a power of 80% and a confidence level of 95%, assuming a 20% loss to follow up (Jianjaroonwong, 2013).

Statistical differences in eradication rates among the different regimen were assessed by chi-square test. The demographic data and frequencies of adverse reactions were compared using chi-square test or Fisher's exact test, when appropriate. The p-values < 0.05 were considered to be statistically significant. The statistical analyses were performed using the Stata/SE 10.1.

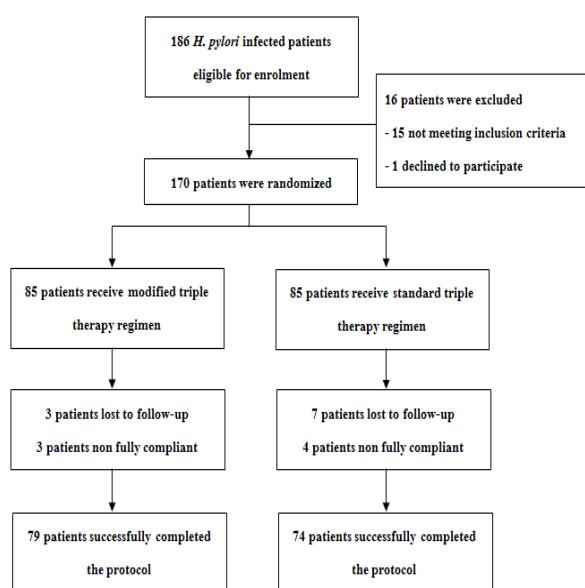


Figure 1. Flow Chart of Patients During the Study

Results

Baseline characteristics of patients

From April to November 2015, 186 patients with *H. pylori* infection from three hospitals were evaluated. Of these patients, 170 were enrolled and randomized to receive one of two regimens. Eighty-five patients were assigned to the MTT group and 85 patients to the STT group. The flow chart of patients included in the study is displayed in Figure 1. No differences were observed between two groups regarding baseline characteristics of patients (Table 1).

Table 1. Baseline Characteristics of Subjects in the Two Treatment Groups

	Modified triple therapy (n = 85)	Standard triple therapy (n = 85)	p-value
Age, mean	54.6	52.4	0.19
Male gender, n (%)	45 (52.9)	40 (47.1)	0.44
BMI	23.8	23.7	0.8
Smoking > 5/day, n (%)	5 (5.9)	9 (10.6)	0.26
Alcohol consumption	1 (1.2)	1 (1.2)	1.00
> 1 day/week, n (%)			
Underlying disease			
Cardiovascular disease, n (%)	3 (3.5)	1 (1.2)	0.62
Diabetes mellitus, n (%)	10 (11.8)	11 (12.9)	0.81
Hypertension, n (%)	16 (18.8)	16 (18.8)	1
Dyslipidemia, n (%)	11 (12.9)	10 (11.8)	0.82
Cirrhosis, n (%)	12 (14.1)	18 (21.1)	0.23
Endoscopic findings			
Chronic Gastritis without atrophy, n (%)	41 (48.2)	39 (45.9)	0.76
Atrophic gastritis, n (%)	10 (11.9)	14 (16.5)	0.4
Erosive gastritis, n (%)	13 (15.3)	9 (10.6)	0.36
Hemorrhagic gastritis, n (%)	15 (17.7)	16 (18.8)	0.84
Gastric ulcer, n (%)	5 (5.9)	8 (9.4)	0.39
Duodenal ulcer, n (%)	4 (4.7)	5 (5.9)	1.00

Table 2. Efficacy of Modified Triple Therapy and Standard Triple Therapy in the Study

	Modified triple therapy	Standard triple therapy	p-value
Intention-to-treat	72/85 (84.7%)	65/85 (76.5%)	0.18
Per protocol	72/79 (91.1%)	65/74 (87.8%)	0.5

Eradication rates of H. pylori infection

The eradication rates by PP and ITT analysis are shown in Table 2. In the MTT group, ITT and PP analyses of the eradication rates were 84.7% and 91.1%, respectively; whereas, the eradication rates in the STT group were 76.5% by ITT analysis and 87.8% by PP analysis. These eradication rates tended to be more successful in the MTT group than those in the STT group; however, it was not statistically significant.

Secondary outcomes

Eighty three patients in MTT group and 85 in STT group completed results of *CYP2C19* genotypes. The prevalence of *CYP2C19* genotypes were similar in each groups with no significant difference ($p = 0.25$), as shown in Table 3. Although this data suggested that the major benefit of the MTT may be in the subgroup of extensive metabolizers, the eradication rates classified by *CYP2C19* genotypes did not differ significantly between the MTT and STT groups (Table 4).

23S rRNA gene of *H.pylori* could be amplified by PCR-RFLP technique in eighty six patient specimens from total of 170 specimens. In these 86 amplifiable specimens, 6 specimens (7.0%) had mutated 23S rRNA gene of *H.pylori* (1 with A2142G A/G, 3 with A2143G A/G and 2 with A2143G G/G) thus the owners were diagnosed to be infected with clarithromycin-resistant strains (Table 5).

Table 3. Prevalence of *CYP2C19* Genotypes

Prevalence of	Modified triple therapy (n = 85)	Standard triple therapy (n = 85)	p-value	All subjects
Extensive metabolizer (EM), n (%)	40 (48.2)	34 (40.0)		74 (44.1)
Intermediate metabolizer (IM), n (%)	38 (45.8)	40 (47.1)	0.25	78 (46.4)
Poor metabolizer (PM), n (%)	5 (6.0)	11 (12.9)		16 (9.5)

Table 4. Outcome of Treatment Classified by *CYP2C19* Genotypes

Eradication rate of	Modified triple therapy (% eradication rate)	Standard triple therapy (% eradication rate)	p-value
Extensive metabolizer (RM)			
ITT	37/40 (92.5%)	28/34 (82.4%)	0.18
PP	37/40 (92.5%)	28/32 (87.5%)	0.48
Intermediate metabolizer (IM)			
ITT	29/38 (76.3%)	27/40 (67.5%)	0.39
PP	29/35 (82.9%)	27/36 (75.0%)	0.42
Poor metabolizer (PM)			
ITT	4/5 (80%)	10/11 (90.9%)	0.54
PP	4/5 (80%)	10/10 (100.0%)	0.14

Table 5. Prevalence of Mutated 23S rRNA Gene of Clarithromycin-resistant *H.pylori*

Mutation	Modified triple therapy n = 37(%)	Standard triple therapy n = 49 (%)	All subjects n = 86
A2142G A/G, n (%)	-	1 (2.0)	1 (1.2)
A2143G A/G, n (%)	1 (2.7)	2 (4.1)	3 (3.5)
A2143G G/G, n (%)	1 (2.7)	1 (2.0)	2 (2.3)
All mutations, n (%)	2 (5.4)	4 (8.2)	6 (7.0)

Table 6. Side Effects of Modified Triple Therapy and Standard Triple Therapy

	Modified triple therapy (n = 75)	Standard triple therapy (n = 75)	p-value
Bitter taste, n (%)	44 (53.7)	49 (62.8)	0.24
Diarrhea, n (%)	0 (0)	3 (3.9)	0.11
Dizziness, n (%)	0 (0)	4 (5.1)	0.05
Headache, n (%)	3 (3.7)	1 (1.3)	0.62
Nausea, n (%)	4 (4.9)	5 (6.5)	0.74
Skin rash, n (%)	0 (0)	0 (0)	-

Side effects and compliance with therapy

Side effects, including bitter taste, diarrhea, dizziness, headache, fatigue, and nausea were all mild and did not lead to significant difference between 2 groups as shown in Table 6. Bitter taste was the most commonly reported adverse effect in both groups (53.7% in the MTT group vs. 62.8% in the STT group; $p = 0.24$). Three patients in the MTT group and 7 patients in the STT group were lost to follow up with unknown reason. Drug compliance with the MTT regimen was 79/85 (92.9%) and 74/85 (87.1%) in the STT group indicating no significant difference ($p = 0.20$).

Discussion

Although the Maastricht IV consensus stated that clarithromycin-containing triple therapy can be recommended for first-line empirical treatment in the areas of low clarithromycin resistance rate (less than 15 - 20%) (Malfertheiner et al, 2012), the most recent data have shown that *H. pylori* eradication rate with triple therapy regimen, including PPI, amoxicillin, and clarithromycin in many regions has declined to 80% or below (Graham and Fischbach, 2010; Jianjaroonwong, 2013; Yoon et al, 2013). When the pattern of antibiotic resistance is unknown, only regimens that are expected to provide eradication rate at least 90% (by ITT analysis) should be prescribed as empiric therapy (Graham et al, 2014). Treatment success with eradication rate greater than 90% by intention-to-treat analysis has been defined as “good” and $\geq 95\%$ as “excellent” outcome (Graham et al, 2007). Factors affecting the eradication rate are antibiotic resistance, *CYP2C19* genotypes, drug regimen, and patient’s compliance. The regimen that can optimize these factors might be a candidate for ideal empiric therapy.

Modified triple therapy regimen is composed of clarithromycin plus three-times-daily dosing of omeprazole, which is aimed to overcome the effect of different *CYP2C19* genotypes in patients, and three-times-daily dosing of amoxicillin, which is more appropriate than twice-daily dose due to its pharmacokinetics. With respect to findings of current study, we found that modified triple therapy was not better than standard triple therapy (twice-daily dosing of omeprazole and amoxicillin plus clarithromycin) as we expected. The prevalence of *CYP2C19* genotypes between these two groups of treatment were not different and were consistent previous study revealing that intermediate and extensive metabolizer were the most common genotypes in northeast of Thailand (Tassaneeyakul et al, 2002). When compared to STT group, *H. pylori* eradication rates in the MTT group seemed to be superior in the extensive and intermediate metabolizers; although, the magnitude of difference was not statistically significant. This result can be explained by the effect of multiple doses of omeprazole that decrease the influence of *CYP2C19* genotype on gastric acid inhibition. Even that the eradication rate of MTT in extensive metabolizers achieved more than 90%, it was surprising that the eradication rate fall below 90 % in intermediate and poor metabolizers. Clarithromycin resistance may be the factor contributing to these low success rates and the three-times-daily dosing of omeprazole and amoxicillin may

not be adequate for patients infected with clarithromycin-resistant *H. pylori*. Although prevalence of clarithromycin-resistant *H. pylori* strains in our study was 7.0%, this result may underestimate the true prevalence because we could not amplified 23S rRNA gene of *H. pylori* in all patient specimens. There was also no difference regarding the safety profiles and patient compliance of these two regimens. According to our results, none of triple therapy regimens can be recommended as the first-line treatment for *H. pylori* infection because their eradication rates were estimated less than 90% by the ITT analysis.

The first limitation of our study was the fact that we could not evaluate the prevalence of clarithromycin resistance in all patients. For this reason, we cannot absolutely conclude that MTT and STT were not effective due to clarithromycin resistance or other factors. Second, we did not monitor intragastric pH in our subjects which can confirm whether three-times-daily dosing of omeprazole was sufficient to control gastric acid in extensive metabolizers. Another limitation is bias from open label study design, so we tried to reduce any potential bias by using randomization and objective measurement of primary outcome.

The modified triple therapy with three-times-daily dose of omeprazole and amoxicillin plus clarithromycin was not superior to standard triple therapy in terms of *H. pylori* eradication. Neither modified triple therapy nor standard triple therapy achieved acceptable eradication rates in this study; therefore, they are not recommended for the population of northeast Thailand. This low success rate may be due to more prevalence of clarithromycin resistance in our area than we expected or inadequacy of PPI and amoxicillin dosage. To explain this result, further studies are recommended to explore the true prevalence of clarithromycin resistance in northeast region of Thailand. If the clarithromycin resistance rate in this region is more than 15 - 20%, clarithromycin-containing triple therapy should be absolutely abandoned, as suggested by Maastricht IV consensus (Malfertheiner et al, 2012). Moreover, if the clarithromycin resistance rate is still low, studies of triple therapy regimen with higher dose of omeprazole and amoxicillin (e.g. four-times-daily dosing omeprazole and amoxicillin) may be needed to test our hypothesis.

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