Original Article

Non-antibiotic Quadruple Regimen for *Helicobacter pylori* Eradication

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ABSTRACT

Background: Antimicrobial resistance and patient compliance are important factors leading to *H. pylori* eradication failure. To avoid such problems, we formulated a new PPI-based non-antibiotic regimen to eradicate *H. pylori*. This concoction comprises of curcumin, probiotics, bismuth subsalicylate and esomeprazole. Curcumin is one of natural substances widely investigated as a potential alternative for treatment of *H. pylori* infection, as it can inhibit adhesion of *H. pylori* to stomach. Bismuth compounds can inhibit growth of *H. pylori*; while probiotics can decrease colonization of this organism.

Aim: To determine the efficacy of a PPI-based non-antibiotic quadruple regimen in *H. pylori* eradication.

Method: Sixteen NUD patients (11 females, mean age 43.5 ± 12.5 years, range 22-63) tested positive for *H. pylori* were enrolled. Patients were administered for 7 days of curcumin 48 mg q.i.d., *Lyophilized live Lactobacillus acidophilus + Bifidobacterium infantis* 2 capsules b.i.d., bismuth subsalicylate 524 mg q.i.d., and esomeprazole 20 mg b.i.d. All patients were evaluated by ^{14}C-urea breath test and gastrointestinal symptom score. Primary and secondary end point was eradication rate and gastrointestinal symptom improvement, respectively.

Result: One of 16 patients (6.25%) was cured of *H. pylori* infection. A significant improvement in overall GI symptom (T0 : median 6, range 1-15; T1: median 2, range 0-11; p = 0.003; T4 : median 2, range 0-11; p = 0.001) was observed at 1 and 4 weeks after treatment.

Conclusion: Our non-antibiotic quadruple regimen was not as effective as standard triple regimen for *H. pylori* eradication, and may need further exploration such as extending the treatment duration or replacing with another probiotic. However, significant improvement in dyspeptic symptoms was observed after 1 and 4 weeks after treatment.

Key words : *H. pylori, quadruple regimen*

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Introduction

Helicobacter pylori is a slow-growing, microaerophilic, highly motile, gram-negative spiral-shaped bacterium, that is attached to gastric mucosa. It is now acknowledged that *H. pylori* is one of the most common human bacterial infectious diseases and is associated with gastritis-associated gastrointestinal diseases, gastric ulcer, duodenal ulcer, gastric cancer and gastric mucosal-associated lymphoid tissue (MALT) lymphoma (MALToma)[1]. The prevalence of *H. pylori* infection varies depending on ethnicity, age and socioeconomic factors. It can be found in 70-90% of population in developing countries and in 25-50% in developed countries[2]. In Thailand *H. pylori* infection was found in 48.2% of dyspeptic patients with high incidence in the age-group 31-60 years (63.7%) and 98.2% of *H. pylori* infection was found to be associated with gastritis[3].

Treatment of *H. pylori* infection requires combinations of antibiotic and additional non-antibiotic adjunctive agents. First-line therapy that is now generally accepted consists of proton pump inhibitor or ranitidine bismuth citrate plus two antibiotics: clarithromycin and amoxicillin. Metronidazole can be used as an alternative to amoxicillin[4]. The average success rate for this traditional triple therapy is approximately 70% (range from 60% to 85%). With these recommended regimens, at least 20% of patients did not achieve eradication in clinical practice[5]. Antimicrobial resistance is a major cause of treatment failure and clarithromycin resistance appears to be the most important mechanism[6]. In Thailand, the prevalence of *H. pylori* that resisted to amoxicillin, clarithromycin, metronidazole, tetracycline, and multi-drugs was 13.9%, 19.0%, 30.4%, 5.1%, and 16.5% respectively[7]. Bismuth based quadruple therapy is a preferred option as second choice treatment of *H. pylori* infection, if not previously used[8]. New antimicrobial drugs such as levofloxacin[9,10] rifabutin[11,12] and furazolidone[13] have been introduced for improve success rate of treatment. Other important factors related to eradication failure include poor compliance and inadequate duration of therapy. Compliance is reduced when there are significant adverse effects. Nausea and diarrhea is the most common side effect and present in almost antibiotics used. Moreover, antibiotic therapy can lead to the development of pseudomembranous colitis and overgrowth of *Candida albicans*[1].

Currently, several naturally occurring substances have been investigated as potential alternatives for the treatment of *H. pylori* infection. Adjuvant therapy such as probiotics, lactoferrin[14], curcumin , mucolytic[15], vitamin C[16], polyunsaturated fatty acid[17], mastic gum[18], garlic[19], berberine[20] and flavonoids[21] are an alternative approach for treatment of *H. pylori* infection[22]. Probiotics are live, non-pathogenic microbial feed or food supplement that can affect the host in a beneficial manner. The best-studied probiotics are currently the lactic acid-producing bacteria, particularly *Lactobacillus* spp. and *Bifidobacterium* spp.[23] Probiotics are now accepted as being useful in prevention and treatment of certain pathological conditions, mainly in small and large intestine. Specific strains of *Lactobacillus* spp. and *Bifidobacterium* spp. exert in vitro bactericidal effects against *H. pylori* through the release of bacteriocins or production of organic acids, and/or inhibit its adhesion to epithelial cells[24]. Clinical trials evaluating the use of different probiotic strains in colonized subjects had been reviewed by Hamilton-Miller[25]. In some of these studies, probiotics were used alone, while in others they were used as adjunctive agents to the classical treatment of *H. pylori* infection. Their results indicated that probiotics generally do not eradicate *H. pylori* but decreased the density of colonization, thereby maintaining lower levels of this pathogen in the stomach; in association with antibiotic treatments. Some probiotics increased eradication rates and/or decreased adverse effects due to the antibiotics[26].

Curcumin is a polyphenolic chemical constituent derived from turmeric (Curcuma longa). Numerous studies have indicated that curcumin has antioxidant and anti-inflammatory properties. Curcumin is able to block two critical cellular events triggered by *H. pylori* infection in epithelial cells: (i) NF-kB activation as well as IL-8 synthesis and (ii) the cellular motogenic response[27]. Curcumin was also found to inhibit adhesion of *H. pylori* to gastric mucosa[28]. Several analogues of curcumin have been identified from other plants source. These include gingerol, paradol, cassumunin, galanals, shougaol, diarylheptanoids, yakuchinones, isoeugenol and dibenzoylmethane[29]. Shougaol, which is extracted from ginger rhizome, can inhibit the growth of *H. pylori* CagA+ strains in vitro and this activity may contribute to its chemopreven-tative effects[30].

Bismuth salt has been used in medicine for over three centuries, particularly in treatment of dyspepsia. The commonly used forms of bismuth are colloidal

bismuth subcitrate (CBS), bismuth subsalicylate (BSS) and ranitidine bismuth citrate (RBC). Bismuth was shown to inhibit growth of *H. pylori*. The mechanism of action that cause bactericidal damage to *H. pylori* is unclear. Eradication rate of bismuth monotherapy ranged from 0-32%[31]. A combination of bismuth compounds with other antibiotics results in enhanced eradication of organism. The efficacy of RBC and PPI-based triple regimen were comparable. The *H. pylori* eradication rate of RBC plus two antibiotics (amoxicillin and clarithromycin) was 83%[32].

Because of increase number of drug resistant and poor compliance due to side effect from antibiotics that reduce *H. pylori* eradication rate, *H. pylori* eradication should be considered in the aspect of risk-benefit. If safer alternative regimens were available to eradicate *H. pylori*, all case of *H. pylori* infection should be treated because of potentially increase risk of gastric cancer. Many non-antibiotic regimens were studied for eradication of *H. pylori*. Francesco DM *et al*. tested the efficacy of curcumin-based triple therapy for eradication of *H. pylori* and showed that the eradication rate was only 12% but there was significant immovement in dyspeptic symptom and gastric inflammation[33]. The aim of the present study was to evaluate the effectiveness of non-antibiotic quadruple regimen, comprise of curcumin, bismuth subsalicylate, probiotics, and esomeprazole for *H. pylori* eradication.

Patients and Methods

Patients

Adult functional dyspepsia patients with normal esophagogastroduodenoscopy (EGD) at Maharaj Nakorn Chiang Mai Hospital were asked to participate in the trial. Patients were excluded from the study if they met one of the following exclusion criteria: previous use of H_2 receptor antagonist, bismuth or PPI within 2 weeks prior to the study, use of probiotic products during the previous month, any diagnosed chronic gastrointestinal disease, immunodeficiency state or received immunosuppressive agents, allergies to drugs used in the study, and pregnancy or lactation. Informed consent was obtained from all participants before enrolled in the study.

Assessment of *H. pylori* status

At first, *H. pylori* infection was documented by positive result of rapid urease test (Pronto Dry, MIC, Switzerland) or histology. After 1 month of treatment, all patients underwent the ^{14}C - urea breath test (Pytest, Tri-med, Thailand) according to the manufacturer's instructions. The breath test was positive for *H. pylori* if the disintegration per minute (dpm) was >199, indeterminate if between 50 and 199 dpm, and negative if <50 dpm. All results were read within two standard deviations with a specificity of 100% and a 95% confidence interval.

Dyspeptic symptoms assessment

Dyspeptic symptoms were assessed by Leeds Dyspepsia Questionnaire (LDQ) at baseline, end of treatment, and four weeks after treatment. The LDQ gave range of score from 0-40 and contained question on epigastric pain, retrosternal pain, regurgitation, nausea, vomiting, belching, early satiety and dysphagia[34]. Likert scale (0-5) was used to assess severity of symptom. Adverse events were also assessed during treatment, at the end of treatment and four weeks after treatment.

Study design

All eligible patients were treated for *H. pylori* infection by a combination of curcumin (2 capsule, q.i.d.), Infloran® (2 capsule, b.i.d., 1 capsule contain Lyophillized live *Lactobacillus acidophilus* and *Bifidobacterium infantis* each separately, 10^9), Gastrobismol® (bismuth subsalicylate; 524 mg, q.i.d.) and esomeprazole (20 mg, b.i.d.) for 1 week. Patients were assessed for dyspeptic symptom and adverse effect at baseline, end of treatment and 4 weeks after treatment. *H. pylori* infection was evaluated at 4 weeks after treatment by urea breath test.

Statistical analysis

Patient's characteristic data was expressed as mean ± standard deviation (SD), median, and percent. Wilcoxon signed rank test was used for comparisons the dyspeptic symptom score before and after treatment. SPSS 12.0 software (SPSS Inc., Chicago, IL) was used for all calculation.

Results

Patient characteristics

Sixteen patients were enrolled into the study. Baseline characteristics of the patients were shown in Table 1.

Table 1. Baseline Characteristics of the patients

Characteristic	Patients (%)
Male	5 (31.3)
Age (yr)	
Mean ± SD	43.5 ± 12.49
Median	41.5
Range	22-63
Occupation	
Government officer	2 (12.5)
Agriculturist	5 (31.3)
Employee	5 (31.3)
Other	4 (25)
Income (Baht/mo)	
<5,000	9 (56.3)
5,001-10,000	2 (12.5)
10,001-15,000	4 (25)
>15,001	1 (6.3)
Alcohol	6 (37.5)
Cigarette	3 (18.8)

Eradication Rate

All enrolled patients were evaluated for *H. pylori* eradication using ^{14}C-UBT cut-off criterion, as previously describe. One out of 16 patients was cured of *H. pylori* infection (6.25%).

Dyspeptic symptom improvement

There was a statistically significant decrease in the overall dyspeptic symptom score (Figure 1) from baseline (T0: median 6, range 1-15) to one week (T1: median 2, range 0-11) and one month after treatment (T4: median 2.5, range 0-11). Epigastric pain (T0: median 2, range 0-4; T1: median 0.5, range 0-4; T4: median 1, range 0-4), belching (T0: 1.5, range 0-3; T1: median 0.5, range 0-3; T4: median 0, range 0-3) and early satiety (T0: median 2.5, range 0-4; T1: median 1, range 0-4; T4: median 1, range 0-4) all showed statistically significant improvement after treatment with non-antibiotic quadruple regimen (Figure 2). All symptom scores were showed in Table 2.

Adverse event

None of the patients complained of any adverse reaction after being treated with our non-antibiotic quadruple regimen, except for mention of dark stool that usually seen after taking bismuth subsalicylate.

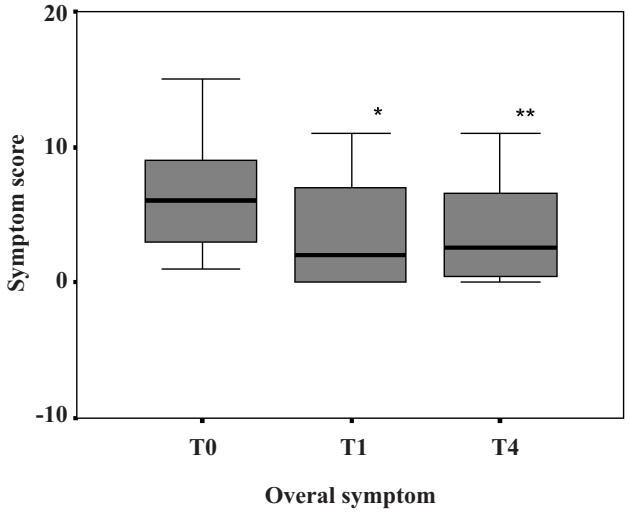

Figure 1. Overall severity of symptom at baseline (T0), end of treatment (T1) and 4 weeks after treatment (T4). Horizontal bar: median; box: 25-75th interquartile range; vertical line: range of value. * p = 0.003, ** p = 0.001

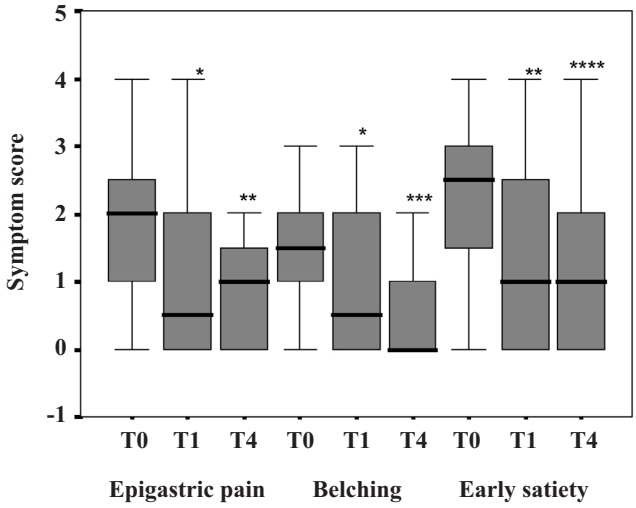

Figure 2. Dyspeptic symptom score of epigastric pain, belching and early satiety at baseline (T0), end of treatment (T1) and 4 weeks after treatment (T4). Horizontal bar: median; box: 25-75th interquartile range; vertical line: range of value. * p = 0.01, ** p = 0.06, *** p = 0.005, **** p = 0.003

Dark stool resolved disapeared after completion of the quadruple therapy course.

DISCUSSION

In this study, we treated dyspeptic *H. pylori*-positive patients with a non-antibiotic quadruple eradica-

Table 2. Symptom score, assessed by LDQ

Symptom	Median			Range		
	Baseline	Week 1	Week 4	Baseline	Week 1	Week 4
Epigastric pain	2	0.5*	1^{+}	0-4	0-4	0-4
Retrosternal pain	0	0	0	0-3	0-1	0-1
Regurgitation	0	0	0	0-2	0-2	0-1
Nausea	0	0	0	0-2	0-1	0-1
Vomiting	0	0	0	0-1	0-1	0-1
Belching	1.5	5*	0$^{\#}$	0-3	0-3	0-3
Ealry satiety	2.5	1^{+}	1†	0-4	0-4	0-4
Dysphagia	0	0	0	0	0	0
Overall	6	2	2.5	1-15	0-11	0-11

*p = 0.01, $^{+}$p = 0.06, $^{\#}$p = 0.005, †p = 0.003

tion regimen. Although this treatment was not effective for *H. pylori* eradication, it resulted significant improvement in dyspeptic symptoms. No adverse effect was observed.

While PPI plays an important role in *H. pylori* eradication, several studies have shown the effect of bismuth subsalicylate, curcumin, and probiotics on treatment of *H. pylori*. The bismuth-based quadruple regimen achieved a better eradication rate compared to PPI-based triple regimens as a first-line eradication option for *H. pylori*[35]. Studies from U.S.[36], Italy[37], and Germany[27], demonstrated in vitro effect of curcumin against *H. pylori*. Probiotics generally cannot eradicate *H. pylori*, but they can decrease the density of colonization. When used as adjunctive therapy, they increase eradication rate and improve compliance due to decreased antibiotic-associated adverse effects[24]. Based on current data, even though certain effect against *H. pylori* has been described, probiotics cannot be considered as an alternative to standard anti-*H. pylori* treatment[38]. In theory, combination of these agents should have beneficial effect on *H. pylori* eradication. Unfortunately, the *H. pylori* eradication rate in our study was only 6.25%.

The failure of H. pylori eradication by this concoction may be from various reasons. First, the effect of curcumin against *H. pylori* seems to be dose dependence. The optimal dose to inhibit growth of *H. pylori* in vivo was unknown. Curcumin dose of 200 mg/day that used in this study might not be sufficient for *H. pylori* eradication. Second, the bismuth and curcumin might reduce the efficacy of probiotics and finally, prolonged duration of treatment might improve the efficacy of this concoction.

One of the sixteen patients had negative ^{14}C-UBT after treatment, but this result should be interpreted cautiously because false negative UBT can be found in currently use proton pump inhibitor, H_2 receptor antagonist, bismuth preparation and antibiotic. Spontaneous remission of *H. pylori* was found in 6.4% of *H. pylori* positive patients, even though they had not received any antibiotics or other treatment[39].

Although this concoction could not eradicate *H. pylori*, the dyspeptic symptom score, especially epigastric pain, belching, and early satiety, showed statistically significant improvement both at the end of treatment and 4 weeks after treatment. Overall symptom score was also showed significant improvement.

Limitation of the current study is that enrolled patients were of only mild to moderate severity of dyspepsia, we could not conclude whether all functional dyspepsia might have benefit from therapy. In addition, this study was an open-label pilot study; then we could not totally exclude placebo effect and observer's bias.

In summary, this concoction which comprises of 1-week administration of curcumin, probiotics, bismuth subsalicylate, and esomeprazole was not effective for *H. pylori* eradication, but appeared to be useful for improving dyspeptic symptoms. The result suggested that currently antibiotics still have an essential role in *H. pylori* eradication. Other agents, whether curcumin or probiotics may have a role as an adjuvant treatment, helping in improving the efficacy or reducing the adverse effect. Further study may also be needed to improve the efficacy of this treatment, such as optimizing the dose and extending the duration of treatment, or switching to other agents.

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