Original Article

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Effect of Bismuth Subsalicylate on Dyspeptic Symptoms and Gastric Histology in *Helicobacter pylori* - negative Gastritis: A Prospective Randomized, Double Blind Placebo Controlled Study

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ABSTRACT

Background: Treatment of patients with dyspepsia and chronic gastritis without *H. pylori* infection remains unsatisfactory. The aim of this study was to determine the effect of bismuth subsalicylate (Gastrobismol®) on symptoms and gastric histology in this group of patients.

Methods: Patients with dyspepsia and chronic *H. pylori* negative gastritis by CLO test® were randomly assigned to receive bismuth subsalicylate or placebo. After four weeks of treatment, three outcomes were analyzed (1) the change from baseline in severity of dyspeptic symptoms (as assessed by the Leeds Dyspepsia Questionnaire), (2) patients' global assessment of efficacy using the proportion of patients without symptoms, proportion of patients with improvement, and proportion of patients who remained unchanged or who deteriorated, and (3) endoscopic appearance and gastric histology.

Results: Forty-five patients were entered and 42 completed the trial (21 patients in the bismuth subsalicylate group and 21 in the placebo group. There was no difference between the two groups in terms of symptom disappearance, total symptoms severity scores, and epigastric pain at the end of treatment. Dyspeptic symptoms of regurgitation, belching and early satiation in the bismuth subsalicylate group were significantly improved from baseline, however, when compared with the placebo group. There was no difference in endoscopic appearance and gastric histology, but gastric body inflammation was significantly decreased in the bismuth group (p=0.04).

Conclusion: Administration of bismuth subsalicylate in patients with dyspepsia and chronic *H. pylori* negative gastritis was of benefit with regard to regurgitation, belching and early satiation symptoms as well as decreased inflammation of the gastric body mucosa.

Key words : Bismuth subsalicylate, dyspepsia, *Helicobacter pylori*

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INTRODUCTION

Dyspepsia is a common chronic condition and a costly problem in primary care and gastroenterology practice. The main symptom of dyspepsia is usually recurrent pain or discomfort in the upper abdomen that impacts negatively on the quality of life. In patients with investigated dyspepsia, 2 main causes are often found, namely structural abnormalities such as chronic peptic ulcer disease, gastroesophageal reflux with or without esophagitis, or malignancy and functional (non-ulcer or idiopathic) dyspepsia[1-3]. The latter is essentially a diagnosis of exclusion. Chronic gastritis from *H. pylori* infection can be diagnosed and successfully treated and up to one third of patients may develop functional dyspepsia. However, there is very little data on chronic gastritis without *H. pylori* infection.

Pharmacologic treatment for patients with functional dyspepsia remains unsatisfactory. Results in controlled trials have generally been disappointing, with only small benefits over the placebo in some studies with histamine H_2-receptor antagonists, proton-pump inhibitors, and *H. pylori* eradication[4]. Several randomized controlled trials and some meta-analyses have demonstrated the superiority of bismuth salt, but such studies mostly evaluated *H. pylori* positive patients and the efficacy of *H. pylori* eradication in functional dyspepsia with marginal statistical significance[5-13]. Bismuth subsalicylate contains 42% salicylate and 58% bismuth. The therapeutic effects of bismuth subsalicylate in gastritis and gastric and duodenal ulcer have been primarily attributed to demulcent and cytoprotective properties. Bismuth subsalicylate interferes with the integrity of the *H. pylori* cell wall and prevents adhesion of the organism to the gastric epithelium. Previous study demonstrated that patients with non-ulcer dyspepsia and histological gastritis (including from *H. pylori* infection) benefited from therapy with colloidal bismuth subcitrate therapy[9].

In this study, we aimed to assess the efficacy of bismuth subsalicylate in *H. pylori* negative patients with dyspepsia, in terms of symptom improvement and gastric histology compared with placebo.

Study design and Patient population

Patients

Outpatients attending gastrointestinal clinics of Maharaj Nakorn Chiang Mai Hospital with dyspepsia (on the basis of the Rome lll criteria) between December 2010 and December 2011 were invited for the study. Dyspepsia was diagnosed if persistent or recurrent upper abdominal pain or discomfort was present. Discomfort was characterized by the presence of one or more symptoms including pain, burning, postprandial fullness or early satiety, and epigastric location over the past 3 months, with symptom onset at least 12 months prior to diagnosis. All patients underwent upper endoscopy and were found to have gastritis (erythema, erosion) and negative urease test (CLO® test). Patients were asked to complete validated questionnaires (LDQ: Leeds Dyspepsia Questionnaire)[14], and patients' global assessments were made after a written informed consent was obtained. Patients were 18 to 80 years of age and were able to provide a written informed consent. Exclusion criteria were pregnancy, liver cirrhosis or presence of gastroesophageal varices, gastrointestinal hemorrhage, peptic ulcer, gastric cancer, reflux esophagitis, irritable bowel syndrome, and ingestion of any medication capable of causing dyspepsia (e.g. NSAIDs, antibiotics, hormone, bronchodilators, and cardiovascular drugs).

Methods

For patients who had previously prior taken PPI, H_2 receptor antagonist, or domperidone, there was a washout period of 4 weeks for PPI and 2 weeks for H_2 receptor antagonist and domperidone. During the washout period, veragel DMS (aluminium hydroxide and magnesium carbonate co-precipitate (325 mg), dimethylpolysiloxane (10 mg), dicyclomine HCl (2.5 mg)) was allowed as a rescue medication. Life style modifications were explained to every patient. Upper endoscopy with urease (CLO®) test was preformed. Patients with gastritis and negative CLO® test were eligible and completed the LDQ.

Randomization code using block of four methods was generated into two arms: the treatment group with bismuth subsalicylate (Gastrobismol® (524 mg)) 2 tabs twice daily for 4 weeks and the placebo group.

Assessment

Symptoms and Global Relief

The validated Leeds Dyspepsia Questionnaire (LDQ)[14] was used to assess dyspeptic symptoms at baseline and after four weeks of treatment. The LDQ, administered by a research nurse in a face-to-face in-

terview, measures eight dyspepsia symptoms on a six-grade scale grade 0 not present, 1=very mild, 2= mild, 3=moderate, 4=severe, and 5=very severe. A summary score with a range of 0 to 40 represents the severity of dyspepsia at baseline and at 4 weeks after treatment. Patients' global assessments of efficacy were evaluated at 4 weeks with the use of a three-grade global scale: symptom-free, improved, and unchanged or deteriorated.

Endoscopic appearance and gastric histology

At endoscopy the gastric body and the gastric antrum were assessed as normal or inflamed. The mucosa was said to be inflamed if erythema, petechiae and/or erosions were present.

Gastric biopsy was taken from the body, the angle and the antrum, both at baseline and the post-treatment endoscopies. Histological gastritis was diagnosed and its severity indicated according to the Sydney classification[15].

Statistical analysis

All statistical analyses were performed using SPSS statistical software version 17.0.0. For nominal data, values were presented as frequencies and proportions. All numerical data were shown as means and standard error. Wilcoxon's signed rank test and *t*-test were used to analyze changes within subjects from the baseline values. All *p*-values presented were 2-tailed and a significance level of 0.05 was used for each comparison.

RESULTS

Patient characteristics

Forty-two dyspeptic patients without *H. pylori* infection were included. All had endoscopic gastritis and were randomized to the bismuth group (21 patients) and the placebo group (21 patients). Demographic characteristics were shown in Table 1. There were no statistically significant differences between the control and the bismuth groups regarding sex, age, BMI, smoking, alcohol consumption, co-morbid diseases, type of dyspeptic symptoms, duration of dyspepsia, previous PPI use, endoscopic findings, gastric histology and the degree of gastric inflammation. Dyspeptic symptoms were more frequent in the bismuth group than in the placebo group (5.7 vs 4.1 days/week, p =0.016).

Effect of bismuth subsalicylate on symptoms response

Twelve patients (28.57%) became totally symptom-free at the end of study, 15 (35.7%) had symptom improvement and 15 (35.7%) were unchanged or deteriorated. There were no significant differences between the bismuth subsalicylate group and the placebo group (p =0.072) with regard to patients' global assessments (Table 2).

Symptom-severity scores by LDQ improved from baseline during treatment in both study groups. In the placebo group, LDQ score was significantly improved from baseline (mean LDQ=7.5±1.2) to post-treatment (mean LDQ=3.6±1.8; p<0.001). In the bismuth subsalicylate group, LDQ score was significantly improved from baseline (mean LDQ=7.9±3.8) to post-treatment (mean LDQ=4.3±4.3) (p<0.001). There was no difference between group in post-treatment LDQ score (p =0.501) (Figure 1).

According to LDQ, epigastric pain improved significantly in the placebo group (p<0.001), while epigastric pain, regurgitation, belching and early satiation were also significantly improved (p <0.001, p =0.049, p =0.01, p =0.031 respectively) (Figure 2).

Effect of bismuth subsalicylate on endoscopic appearance

At the end of study, the endoscopic findings of the gastric body in the placebo group were normal in 11 patients (52.4%), erythema in 9 patients (42.9%) and erosion in 1 patient (4.8%), which in the gastric antrum, the finding were normal in 6 patients (28.6%), erythema in 7 patients (33.3%) and erosion in 8 patients (38.1%). In the bismuth group, the endoscopic findings of the gastric body were normal in 14 patients (66.7%), erythema in 6 patients (28.6%) and erosion in 1 patient (4.8%), gastric while in the antrum the findings were normal in 11 patients (28.6%), erythema in 3 patients (14.3%) and erosion in 7 patients (33.3%). There was no significant difference of endoscopic appearance of gastric body and antrum at baseline and post-treatment in the placebo group (p =0.655 and p =0.739, respectively). Similar findings were noted in the in bismuth subsalicylate group (p =0.48 and p =0.83, respectively).

Effect of bismuth subsalicylate on gastric histology

There were no significant differences between

Table 1. Baseline characteristics of patients.

	Placebo (n=21)	Bismuth (n=21)	*p*-value
Age, year (mean±SD)	51.3±13.6	46.1±12.4	0.204
Female (%)	13 (61.9%)	11 (52.4%)	0.533
BMI (mean±SD)	22.3±3.1	21.7±2.9	0.532
Smoking (%)	5 (23.8%)	9 (42.3%)	0.190
Alcohol drinking (%)	5 (23.8%)	11 (52.4%)	0.057
Co-morbid disease (%)	10 (47.6%)	9 (42.3%)	0.757
Dyspepsia (%)			
Epigastric pain	7 (33.3%)	6 (28.6%)	0.739
Epigastric burning	11 (52.4%)	9 (42.9%)	0.537
Postprandial fullness	5 (23.8%)	7(33.3%)	0.495
Early satiation	2 (9.5%)	1 (4.8%)	1.000
Duration, month (mean±SD)	30.4±39.9	28.5±32.5	0.870
Frequency, times/week (mean±SD)	4.1±2.0	5.7±2.0	0.016
Previous PPI use (%)	21 (100%)	20 (95.2%)	1.000
LDQ (mean±SD)	7.7±3.2	7.9±3.8	0.896
Endoscopic finding (%)			
Gastric Body			
normal	11 (52.4%)	12 (57.1%)	
erythema	10 (47.6%)	7 (33.3%)	0.365
erosion	0	2 (9.5%)	
Gastric Antrum			
normal	5 (23.8%)	5 (23.8%)	
erythema	10 (47.6%)	9 (42.9%)	1.000
erosion	6 (28.6%)	7 (33.3%)	
Gastric histology (%)			
Gastric Body			
normal	2 (9.5%)	8 (38.1%)	0.067
chronic superficial gastritis	19 (90.5%)	13 (61.9%)	
Gastric Antrum			
normal	2 (9.5%)	1 (4.8%)	
chronic superficial gastritis	15 (71.4%)	16 (76.2%)	1.000
chronic atrophic gastritis	4 (19.0%)	4 (19.0%)	
Gastric inflammation (%)			
Gastric body, neutrophils	7 (33.3%)	8 (38.1%)	1.000
Gastric antrum, neutrophils	9 (42.8%)	12 (55.2%)	0.364

Table 2. Patients' global assessments.

	Placebo (n=21)	Bismuth (n=21)	*p*-value
Symptoms free	7 (33%)	5 (23.8%)	0.495
Improved	4 (19%)	11 (52.4%)	0.024
Not improved	10 (47.6%)	5 (23.8%)	0.107

baseline and post treatment gastric histology of the body and the antrum in the placebo group (p =0.317 and p =1.0, respectively), as well as in the bismuth subsalicylate group (p =1.0 and p =1.0, respectively). Gastric inflammation, however, was significantly decreased in the gastric antrum in both groups (p =0.034 in the placebo group, p =0.025 in the bismuth subsalicylate group), while, gastric body inflammation was significantly decreased in the bismuth group compared with the placebo group (p =0.04).

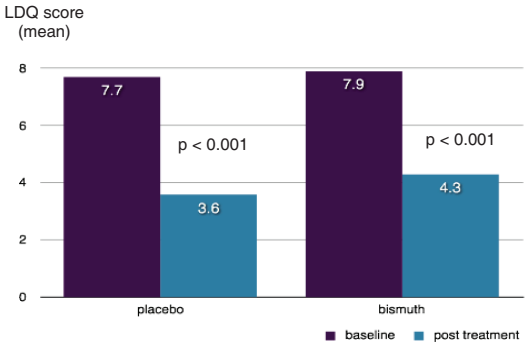

Figure 1. Comparisons of baseline and post-treatment summary scores for symptom severity based on the Leeds Dyspepsia Questionnaire (LDQ).

Patient compliance and drop outs

Fourty-two of 45 patients completing the study took more than 80% of the prescribed medication. Three patients (2 from the placebo group and 1 from the bismuth group) were excluded from analysis using to defaulted follow up.

Adverse events

Adverse events during treatment were reported in 1 patient (4.76 %) in each group. No difference in the overall incidence of adverse events was observed between the two study groups. Side effects included skin rash in the bismuth group and mouth swelling in the placebo group, which were not serious and disap-

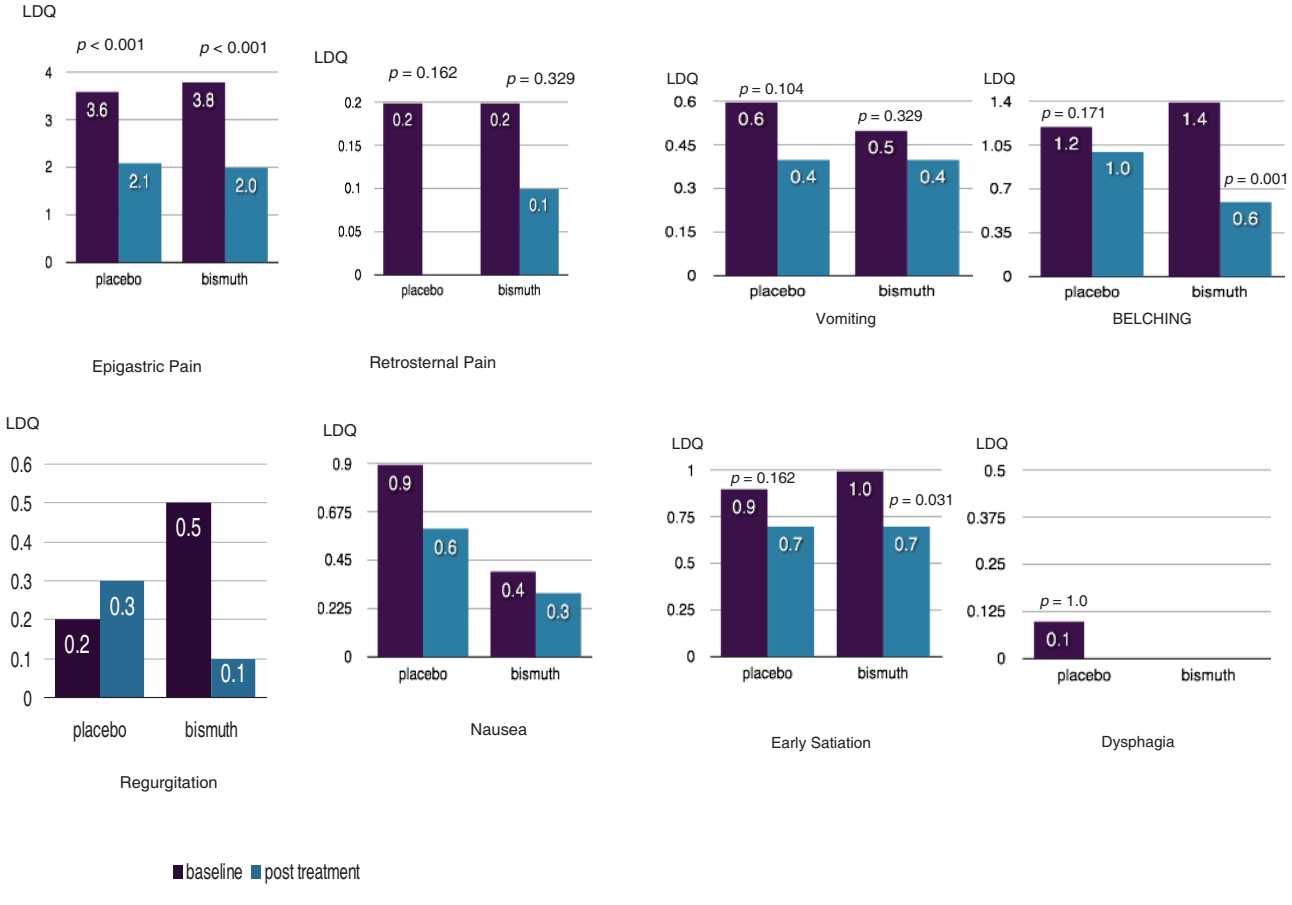

Figure 2. Comparisons of baseline and post-treatment severity for each symptom, based on the Leeds Dyspepsia Questionnaire (LDQ).

peared at the end of study follow up.

DISCUSSION

Dyspepsia is a common chronic gastrointestinal disorder. Overall, the only therapies with established efficacy in functional dyspepsia are *H. pylori* eradication and PPI therapy as recommended by AGA[16-17]. Responses to other treatments are varied. Bismuth subsalicylate is an over-the-counter medication for dyspepsia, heartburn, and nausea. It is also used to treat diarrhea and to prevent travelers' diarrhea as well as for *H. pylori* eradication. The results from our study showed that bismuth subsalicylate improved dyspeptic symptoms of regurgitation, belching and early satiety, as well as significantly compared to decreasing gastric body inflamation compared to placebo. Bismuth subsalicylate should thus be considered for the treatment of dyspepsia, especially for epigastric pain, regurgitation, belching, and early satiety.

Three-fourth of patients exhibited symptom improvement, while one-fourth was symptom-free after bismuth therapy for four weeks. All patients had improved LDQ score, including patients in the controlled group, as noted in the previous studies[7]. A systematic review demonstrated inadequate evidence that prokinetic therapy was effective in functional dyspepsia (RR, 0.52; 95% CI, 0.37-0.73) while H_2RA could significantly reduce symptoms (RR, 0.78; 95% CI, 0.65- 0.93)[4]. However, there was heterogeneity in the study and methodology quality in that review. There are insufficient data to evaluate the efficacy of antidepressants in functional dyspepsia. One small double-blind crossover trial involving 7 patients reported that dyspepsia improved in 5 of 7 patients (71%) taking amitriptyline 50 mg at night compared with 2 of 7 (28%) taking placebo (RR, 0.4; 95% CI, 0.11-1.21; p= 0.29)[18]. Each study demonstrated a placebo effect of about 20-30%, similar to that in our study.

Although the endoscopic findings in the antrum and the body of stomach after bismuth therapy were not significantly changed, gastric inflammation at the antrum decreased significantly after bismuth therapy for four weeks. Our study confirmed the anti-inflammatory effect of bismuth for *H. pylori* negative gastritis, just as the case for *H. pylori* positive gastritis. This helps explain the efficacy of bismuth in patients with *H. pylori* negative gastritis.

In conclusion, four weeks of bismuth therapy improve dyspeptic symptom especially epigastric pain, regurgitation, belching, and early satiety in chronic *H. pylori* negative gastritis patients. The mechanism for the efficacy of bismuth remains intriguing.

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