Effectiveness of Ranitidine Bismuth Citrate Based Triple Therapy for Treating *Helicobacter pylori*

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Abstract

Objective : To determine the efficacy, safety and tolerance of a one week regimen of RBC, clarithromycin, and amoxicillin for *H. pylori* eradication in Thai patients.

Material and Method : Patients who were undergoing endoscopy for dyspeptic symptoms. On the day of endoscopy, three biopsies were taken for *H. pylori* diagnosis. The patients who had the presence of *H. pylori* infection by positive from rapid urease test or histologic examination were invited to take part in an open, prospective study. Patients received a combination of RBC 400 mg, clarithromycin 500 mg, and amoxicillin 1 g twice daily for 7 days. Repeated endoscopy was performed to evaluate *H. pylori* eradication at least 1 month after the end of treatment. Clinical symptoms, side effects and compliance were assessed by interview during the study and at follow-up.

Results : Thirty nine patients with *H. pylori* infection were included. Male and female rates was 27 : 12 with a mean age of 42.8 ± 11.4 years (range 21-68). There was a 89.74 per cent eradication rate by intent-to-treat and 94.59 per cent by per-protocol analysis. There were no serious adverse events during the study. Two patients (5.13%) stopped the medication because of side effects. Two patients had failure to eradication after complete treatment. Subjective improvement of the clinical symptoms was found in 92.3 per cent.

Conclusion : One week's regimen of RBC, clarithromycin, and amoxicillin triple therapy resulted in a relatively high efficacy, safety and tolerance for *H. pylori* eradication in Thai patients.

Key word : Ranitidine Bismuth Citrate, Triple Therapy, *Helicobacter pylori*

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The discovery that peptic ulcers can be caused by gastroduodenal infection with *Helicobacter pylori (H. pylori)* and cured by eradication of this bacterial presence has made a profound impact on ulcer management[1-4]. Although many combination therapies have been proposed to treat *H. pylori* infection, there is still interest in identifying a simple and inexpensive regimen with safety, tolerability, and high rates of success in *H. pylori* eradication.

Classical bismuth based triple therapy has good eradication of *H. pylori* but this therapeutic efficacy is limited by a somewhat high incidence of side effects[5]. Ranitidine-bismuth-citrate (RBC) is a relatively new antimicrobial agent that was developed for the purpose of treating *H. pylori* infection [6,7]. RBC has been shown *in vitro* to have both inhibitory and bactericidal activity against *H. pylori*. RBC has approximately a twofold greater anti *H. pylori* activity than an equivalent mixture of ranitidine with bismuth citrate, which is possibly due to the greater solubility of RBC even at lower pH values[6].

The combination of ranitidine-bismuth-citrate (RBC) 400 mg twice daily for 4 weeks, with clarithromycin 500 mg three times daily for 14 days, is a regimen approved by the U.S. Food and Drug Administration for the eradication of *H. pylori*, which has been shown to have a *H. pylori* eradication rate of (78-84%) in several trials[8,9]. The dual therapy regimen including RBC had on average a higher rate of treatment success than the dual therapy regimen including proton pump inhibitors[10]. Although the dual therapy regimens have good compliance with a low incidence of side effects, they have less than desirable eradication rates.

Triple therapy with proton pump inhibitor/ RBC, clarithromycin and either amoxicillin or a nitroimidazole are widely accepted as treatment for *H. pylori* infection that have provided 85-95 per cent eradication in most studies[11-13]. There is no reported data about *H. pylori* eradication by RBC based triple regimens in Thailand. Therefor, the present study was designed to determine the efficacy, safety and tolerance of one week's regimen of RBC, clarithromycin, and amoxicillin for *H. pylori* eradication in Thai patients.

MATERIAL AND METHOD

The authors studied patients aged between 18 and 80 years who were undergoing endoscopy for the investigation of dyspeptic symptoms. All patients had never received *H. pylori* eradication therapy. Patients who were unwilling to give written informed consent, who were pregnant or lactating were excluded. All patients had no history of hypersensitivity to RBC, amoxicillin and clarithromycin. On day of endoscopy three biopsies were taken for *H. pylori* diagnosis: a single antral biopsy for rapid urease test (CLO test® from Delta West Ltd., Western Australia) and antral and corpus biopsies for histologic examination (hematoxylin and eosin and Giemsa stains). The patients who had a presence of *H. pylori* infection were invited to take part in an open, prospective study. Therapy was initiated the day after endoscopy in all cases, and patients received a combination of RBC 400 mg, clarithromycin 500 mg, and amoxicillin 1 g twice daily for 7 days. Patients were scheduled, after finishing the treatment period, to assess adverse events and compliance. Repeated endoscopy was performed to evaluate *H. pylori* eradication and considered eradicated when the rapid urease test and histology results were negative at least 1 month after the end of treatment. At follow-up, improvement of symptoms were recorded on a scale of the same symptoms, some improvement and marked improvement. Side effects and compliance were also assessed by interview during the study and at follow-up. The *H. pylori* eradication rate was calculated as the percentage of patients whose *H. pylori* were undetectable after treatment.

RESULTS

Thirty-nine patients who presented with *H. pylori* infection were included in the study. There were twenty-three patients with gastritis and sixteen patients with duodenal ulcer. Male and female ratio was 27 : 12 with a mean age of 42.8 ± 11.4 years (range 21-68). Of the 39 patients, 35 were negative for *H. pylori*, resulting in an 89.74 per cent eradication rate by intent-to-treat and 94.59 per cent by per-protocol analysis. In the duodenal ulcer group, the eradication rate by intent-to-treat was 93.75 per cent and 100 per cent by per-protocol analysis. In the non-ulcer dyspepsia group, the eradication rate by intent-to-treat was 86.96 per cent and 90.91 per cent by per-protocol analysis, respectively (Table 1). There were no serious adverse events during the study. Two patients (5.13% overall) reported the side effects of headache and bitter taste. These patients stopped their medication. Two patients had failure of eradication

Table 1. Eradication rate by intention to treat and per protocol analysis in all groups.

	ITT	PP
Total (n=39)	89.74	94.59
Duodenal ulcer (n=16)	93.75	100
Non-ulcer dyspepsia (n=23)	86.96	90.91

ITT = indicates intention to treat
PP = indicates per protocol

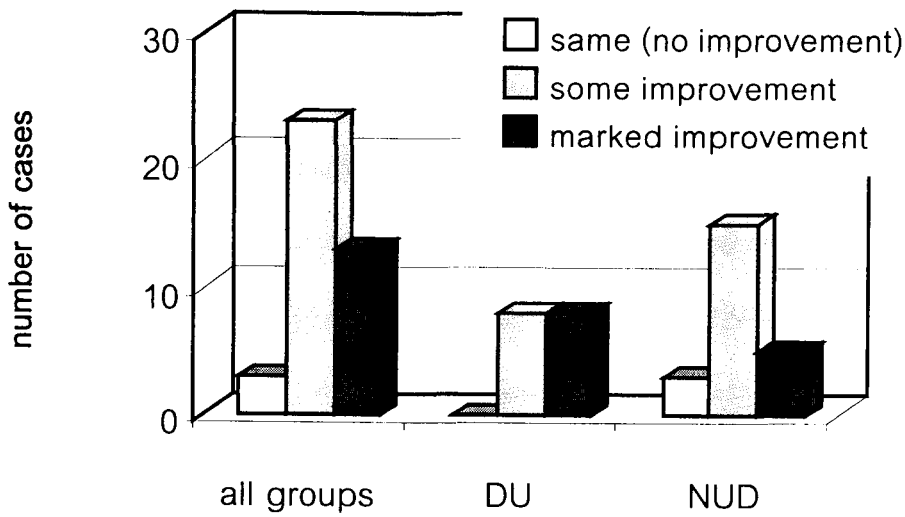
after complete treatment. Subjective improvement of the clinical symptoms was found in 92.3 per cent (Fig. 1).

DISCUSSION

There has been uniform agreement from consensus conferences worldwide that all peptic ulcer patients who are infected by *H. pylori* should be given treatment to eradicate the organism[2,14]. Marked reduction in ulcer recurrence following eradication of *H. pylori* has been firmly established[4,15]. Ranitidine bismuth citrate (Pylorid, Glaxo-Wellcome) (RBC) is a relatively new compound developed for the eradication of *H. pylori*, which possesses the antisecretory activity of ranitidine and the mucosal protective and anti-*H. pylori* effects of other bismuth salts[16]. RBC suppresses growth of *H. pylori*, and has a specific inhibitory effect on the bacterial motor mechanism.

RBC is a novel salt of ranitidine which provides a unique combination of properties: inhibition of secretion of gastric acid by competitive antagonism of the action of histamine at the histamine H_2-receptor on the gastric parietal cell, mucosal protective effects and anti-*H. pylori* action. Ranitidine bismuth citrate provides effective healing and symptom relief, both in duodenal ulcer disease and in gastric ulcer disease. When coprescribed with certain antibiotics (clarithromycin alone or combined with amoxicillin or nitro-imidazole), it heals ulcers, eradicates *H. pylori* and prevents recurrence of the disease. Moreover, RBC has both inhibitory and bactericidal activity against *H. pylori in vitro* and it has been postulated that it may also decrease the development of antibiotic resistance by *H. pylori* [17].

A synergy between RBC and clarithromycin may exist *in vivo*, while clarithromycin resistance is increasing. RBC based triple therapy was unaffected by metronidazole susceptibility and achieved



DU = indicates duodenal ulcer
NUD = indicates non-ulcer dyspepsia

Fig. 1. Illustrates the improvement of symptoms after treatment.

a significantly higher eradication rate in metronidazole-resistant cases than the omeprazole based therapy[18,19].

The safety profile of currently approved bismuth preparations, such as tripotassium dicitrato bismuthate (De-Nol), bismuth subsalicylate (Pepto-Bismol) and ranitidine bismuth citrate (Pylorid), is excellent. Adverse reactions to these agents are mild, transient and infrequent, and reports of serious adverse reactions are rare. Less than 1 per cent of the bismuth dose administered is absorbed. During repeated dosing with ranitidine bismuth citrate 200, 400 or 800 mg b.d. trough plasma bismuth concentrations remain well below 50 μg/L[20]. After discontinuation of treatment with bismuth preparations its excretion in urine may continue for up to 3 months, by which time blood bismuth concentrations have declined to pretreatment values. This regimen was well tolerated although two of the patients suspended the treatment because of side effects. Only mild to moderate side effects were reported during the study. The complaint symptoms were headache and bitter taste. However, most regimens were well tolerated, with only mild to moderate side effects reported[7]. RBC alone is well tolerated and, even when given with clarithromycin. The side effects associated with the treatment regimen used in this study were probably due to either RBC or clarithromycin or both.

The present results showed a lower eradication rate in patients with histologic gastritis than in peptic ulcer patients. The explanation for this is not clear but it might be due to the fact that higher grades of inflammation in the antrum were associated with higher eradication rates and functional dyspepsia may be associated with a lower degree of inflammation. In summary, a combination of RBC 400 mg, clarithromycin 500 mg, and amoxicillin 1 g twice daily for 7 days is a simple, well-tolerated and high efficacy regimen for the eradication of *H. pylori.*

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ประสิทธิผลของสูตรยารานิทิดีน บิสมัธ ซิเตรท ในการกำจัดเชื้อ*เฮลิโคแบคเตอร์ ไพลอริ*

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วัตถุประสงค์ : เพื่อศึกษาผลของสูตรยารานิทิดีน บิสมัธ ซิเตรทร่วมกับ clarithromycin และ amoxicillin เป็นเวลา 1 สัปดาห์ ในการกำจัดเชื้อ*เฮลิโคแบคเตอร์ ไพลอริ*

วัสดุและวิธีการ : ศึกษาในผู้ป่วยที่มารับการตรวจส่องกล้องทางเดินอาหารส่วนต้นด้วยเรื่องไม่สบายในท้อง โดยทำการตรวจหาเชื้อ*เฮลิโคแบคเตอร์ ไพลอริ* ด้วยการทำ rapid urease test และการตรวจชิ้นเนื้อทางพยาธิวิทยา ในรายที่มีการติดเชื้อจะได้รับการเชิญเข้าร่วมการศึกษานี้ โดยได้รับยารานิทิดีน บิสมัธ ซิเตรท 400 มิลลิกรัมร่วมกับ clarithromycin 500 มิลลิกรัม และ amoxicillin 1 กรัม รับประทานวันละ 2 ครั้งเป็นเวลา 1 สัปดาห์ ได้ทำการส่องกล้องทางเดินอาหารและตรวจเชื้อซ้ำหลังหยุดยาแล้วไม่น้อยกว่า 1 เดือน ทำการสัมภาษณ์เพื่อดูอาการ และผลข้างเคียงจากยาในระหว่างทำการศึกษา

ผลการศึกษา : ผู้ป่วยเข้าร่วมการศึกษา 39 คน เป็นชาย 27 คน เป็นหญิง 12 คน อายุเฉลี่ย 42.8 $\pm$ 11.4 ปี (ระหว่าง 21-68 ปี) ผลในการกำจัดเชื้อ*เฮลิโคแบคเตอร์ ไพลอริ* วิเคราะห์โดยวิธี intent-to-treat คิดเป็น 89.74% วิเคราะห์โดยวิธี per protocol คิดเป็น 94.59% มีผู้ป่วย 2 คน (5.13%) รายงานผลข้างเคียงคือ ปวดศีรษะ และขมปาก และได้หยุดยาเองก่อนครบกำหนด มีผู้ป่วยอีก 2 ราย ยังคงตรวจพบเชื้อ*เฮลิโคแบคเตอร์ ไพลอริ* แม้ได้รับยาครบกำหนดก็ตาม อาการไม่สบายในท้องของผู้ป่วยส่วนใหญ่ดีขึ้นบ้างถึงดีขึ้นมาก (92.3%)

สรุป : สูตรยารานิทิดีน บิสมัธ ซิเตรทร่วมกับ clarithromycin และ amoxicillin เป็นเวลา 1 สัปดาห์ มีผลดีในการกำจัดเชื้อ*เฮลิโคแบคเตอร์ ไพลอริ* โดยพบผลข้างเคียงไม่มาก และมีความปลอดภัยจากการใช้ยา

คำสำคัญ : รานิทิดีน บิสมัธ ซิเตรท, *เฮลิโคแบคเตอร์ ไพลอริ*

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