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• *BRIEF REPORTS* •

One-week dual therapy with ranitidine bismuth citrate and clarithromycin for the treatment of *Helicobacter pylori* infection in Brazilian patients with peptic ulcer

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Abstract

AIM: To assess the efficacy and safety of ranitidine bismuth citrate plus clarithromycin given for 1 wk in Brazilian patients with peptic ulcer.

METHODS: One hundred and twenty patients with peptic ulcer were randomized in two treatment groups: (1) 1-wk regimen consisting of ranitidine bismuth citrate 400 mg b.i.d. with clarithromycin 500 mg b.i.d. or (2) 2-wk regimen of the same treatment. Eradication of the infection was considered when both the histologic examination and the urease test were negative for the infection 3 mo after treatment.

RESULTS: By intention to treat analysis, *Helicobacter pylori* (*H pylori*) was eradicated in 73% and 76% of patients, respectively treated for 1 or 2 wk ($P>0.05$). By per protocol analysis, the eradication rates were 80% and 83%, respectively, in patients treated for 1 or 2 wk ($P>0.05$). Nine patients (8.2%) reported minor side effects.

CONCLUSION: One-week therapy with ranitidine bismuth citrate and clarithromycin is safe, well tolerated and effective for treatment of *H pylori* infection, and appears to be comparable to the 2-wk regimen in terms of efficacy.

Key words: *Helicobacter pylori*; Ranitidine bismuth citrate; Clarithromycin; Peptic ulcer

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INTRODUCTION

It is now well established that all patients with peptic ulcer disease and *Helicobacter pylori* (*H pylori*) infection need to be treated in order to eradicate the bacteria[1]. The cure of the infection has proved to accelerate ulcer healing and markedly decreases ulcer relapse[2]. A great number of different therapeutic regimens have been evaluated in the eradication of *H pylori*, but the ideal treatment has not yet been determined. It has been recommended that eradication regimens should achieve cure rates of at least 80%[3]. Triple therapy using proton pump inhibitor with two antibiotics given for 7 d has proved to meet this recommendation[4]. Dual therapy using ranitidine bismuth citrate (RBC) with clarithromycin has also shown to be effective against the infection. RBC associates the antisecretory properties of ranitidine with the antibacterial and mucosal protection properties of bismuth salts. High eradication rates have been reported with the combination of ranitidine bismuth citrate with either clarithromycin for 14 d[5,6] or two antibiotics for 7 d[7-9]. More recently, it has been proposed that satisfactory eradication rates of *H pylori* could also be achieved with the administration of the association RBC-clarithromycin for only 1 wk[10].

Studies evaluating the efficacy of the combination of RBC-clarithromycin in developing countries, which have a high prevalence of *H pylori* infection, are scarce. Considering the potential advantages of an efficient 7-d dual therapy, such as lower cost and better compliance, the aim of this study was to evaluate the efficacy and tolerability of RBC combined with clarithromycin given for either 1 or 2 wk in the eradication of *H pylori* in Brazilian patients with peptic ulcer.

MATERIALS AND METHODS

Patients

This randomized and open study was carried out in 120 patients referred to the gastroenterology clinics of the Campinas University Hospital. The majority of patients seen

at this hospital are of low socioeconomic status. All patients had endoscopy showing duodenal or gastric ulcers associated to *H pylori* infection. The ulcers were either active or healed.

Exclusion criteria were: previous surgery; treatment with proton pump inhibitors, antibiotics or bismuth in the previous month; malignancies; and the presence of esophagitis detected during the endoscopy.

The protocol was approved by the institutional ethics committee. Each patient gave written informed consent before participation in the study.

Study design

Patients were randomized in one of the following two groups: (1) 1-wk regimen consisting of RBC 400 mg b.i.d. with clarithromycin 500 mg b.i.d. or (2) 2-wk regimen consisting of RBC 400 mg b.i.d. with clarithromycin 500 mg b.i.d. The medications of the study were supplied by Glaxo Wellcome Laboratories.

After *H pylori* eradication therapy patients continued using RBC until completing 4 wk of treatment. At the follow-up visit patients were asked about their drug compliance and the occurrence of side effects. Satisfactory compliance was defined as intake of more than 80% of the prescribed dose. Control endoscopy was performed 3 mo after the treatment of the infection.

H pylori assessment

The presence of *H pylori* was assessed by histological examination and urease test after endoscopic biopsies were taken from the antrum and corpus. *H pylori* eradication was considered to be successful when these two tests were negative at the time of the control endoscopy.

Statistical analysis

The intention to treat (ITT) analysis included all randomized patients. In the per protocol analysis, only patients who had taken 80% or more of the medication and had the follow-up endoscopy were included. Statistical significance was calculated using the χ^2-test, Fischer's exact test and Mann-Whitney test, as appropriate. P values less than 0.05 were considered to be statistically significant.

RESULTS

Demographic characteristics of study patients

Sixty-two patients were randomized to receive RBC plus clarithromycin for 1 wk and 58 patients were randomized to receive the 2-wk regimen. Eleven patients did not return for the follow-up visit or second endoscopy. Most of them changed addresses, and could not be located. There was no difference in the age and gender of these patients between the two treatment groups. Overall 56 patients randomized for 1-wk therapy and 53 patients randomized for 2-wk therapy completed the study and were included in the per protocol analysis. All of them reported the use of more than 80% of the medication. The demographic characteristics and diagnosis of the 120 patients are shown in Table 1. The groups of patients receiving each regimen were similar in age, gender, smoking, and proportion of either active or healed duodenal and gastric ulcers.

Table 1 Demographic characteristics and diagnosis of the 120 study patients

	1-wk therapy	2-wk therapy
n	62	58
Mean age (range) yr	48±14 (19–72)	50±14 (18–78)
Male gender	36 (58)	30 (52)
Smokers (%)	16 (26)	13 (22)
Duodenal ulcer (*n*/%)	32 (52)	31 (53)
Gastric ulcer (%)	25 (40)	19 (33)
Duodenal and gastric ulcers (%)	5 (8)	8 (14)
Active ulcers (%)	24 (39)	19 (33)

H pylori eradication

Table 2 shows the eradication rates of the infection and the 95% CI for the two therapeutic regimens. By intention to treat analysis, *H pylori* was eradicated in 73% of patients treated with RBC plus clarithromycin for 1 wk and in 76% of patients treated for 2 wk (P>0.05). By per protocol analysis, the eradication rates were 80% and 83%, respectively, for the 1-wk or 2-wk regimens (P>0.05). Table 3 shows that age, gender, smoking habit and ulcer type were similar in patients with eradicated or non-eradicated infection.

Table 2 Eradication rates and 95% confidence intervals in the two treatment groups

	Eradication rate	95%CI (%)
Intention to treat		
1-wk group (%)	45/62 (73)	62–84
2-wk group (%)	44/58 (76)	65–87
Per protocol		
1-wk group (%)	45/56 (80)	70–91
2-wk group (%)	44/53 (83)	73–93

Table 3 Demographic data and diagnosis in patients with eradicated or non-eradicated *H pylori* infection

	Eradicated infection n = 89	Non- eradicated n = 20
Male gender (%)	44 (49)	12 (60)
Age (yr)	49±14	52±16
Smoking (%)	24 (27)	3 (15)
Duodenal ulcer (%)	46 (52)	10 (50)
Gastric ulcer (%)	34 (38)	7 (35)
Duodenal and gastric ulcers (%)	9 (10)	3 (15)

Data of the control endoscopy

Duodenal and gastric ulcer healing rates were similar for the two treatment groups (Table 4). The control endoscopy showed that two gastric ulcers (one on each treatment group) were incompletely healed. Both patients had their infection eradicated and were non-smokers. In 1 patient treated for 14 d the duodenal ulcer failed to heal. In this case, the patient was a smoker and the *H pylori* infection was not eradicated.

Erosive esophagitis was detected in nine patients (8.2%) in the second endoscopy. None of them had esophagitis in the pre-treatment endoscopy and in all the cases the

esophagitis was mild (Los Angeles grade A). All patients with esophagitis had their *H pylori* infection eradicated ($P>0.05$ in comparison with patients with persistent infection).

Table 4 Data from the control endoscopy

	1-wk	2-wk
Active duodenal ulcer healed (%)	11/11 (100)	7/8 (87.5)
Active gastric ulcer healed (%)	10/11 (91)	10/11 (91)
Esophagitis (%)	5 (8.9)	4 (7.5)

Side effects

Nine patients (8.2%) reported minor side effects, such as disturbances of taste (5 patients), dizziness (1), abdominal pain (2) and mild diarrhea (1). Five of them were treated with the 1-wk regimen. In no case the medication had to be discontinued.

DISCUSSION

The present randomized study assessed the efficacy of the combination ranitidine bismuth citrate and clarithromycin given for 1 or 2 wk in the eradication of *H pylori* in patients with peptic ulcer. Our results indicate that both regimens are safe, healed almost all the active peptic ulcers, and appear to be comparable in terms of *H pylori* eradication rates. The cure rates with intention to treat and per protocol analysis were 76% and 83%, respectively, in patients receiving the 2-wk regimen, and 73% and 80% in those receiving the 1-wk regimen. Reported ITT eradication rates for RBC-clarithromycin given for 14 d ranged from 70% to 96%, with a pooled observed rate of 85%[11]. The eradication rates observed in the current study are therefore within the range reported in the literature. The fact that the cure rates reached with the 2-wk regimen in our patients did not achieve the rates above 90% reported by many authors reinforces the need for local evaluation of the efficacy of treatments. One of the most important factors responsible for failed eradication therapy is the resistance to antibiotics. We did not investigate clarithromycin resistance in our study population, but recent studies in Brazilian patients reported clarithromycin resistance in 7-29% of patients[12-14]. Although previous reports have shown that the association RBC-clarithromycin overcomes the resistance to the antibiotic in most cases[15], this issue merits further investigation in our patients.

There have been only a few studies evaluating the efficacy of the combination of RBC-clarithromycin given for 7 d. The cure rates reported in those studies ranged from 66% to 84% with ITT analysis and 84-90% by per protocol analysis[10,16,17]. The ITT and per protocol eradication rates of 73% and 80% observed in our patients receiving the 1-wk regimen of treatment are therefore in agreement with the reported ranges. The comparison between the two regimens of treatment did not show a statistically significant difference. Similar results were reported by Pozzato *et al*[10], comparing both regimens. Bardhan *et al*[16], observed comparable eradication rates with 7-d RBC-clarithromycin administered alone or with metronidazol.

There is a lack of studies evaluating the efficacy of the 1-wk dual therapy in developing countries. Similar to our observations, one recent open study with 7-d RBC-clarithromycin[18], also from Brazil, reported ITT and per protocol eradication rates of 81% and 86%, respectively. Therefore, our results combined with the data of the literature indicate that 1-wk RBC-clarithromycin could be advantageous, especially in developing countries, due to its lower cost without a significant loss of efficacy in comparison with the 2-wk regimen.

Our results showed that the combination of RBC with clarithromycin is associated to good compliance and few side effects. Only a few patients complained of minor symptoms, and none had to discontinue the treatment.

Previous studies have demonstrated that *H pylori* eradication is sufficient for ulcer healing and relief of symptoms[2], without the need for subsequent therapy. In the present study, after the anti-*H pylori* treatment, RBC was continued until completing 4 wk of the medication, in order to ensure ulcer healing even in those patients in whom eradication therapy failed. Accordingly, the control endoscopy showed ulcer healing in 93% of the cases.

The control endoscopy showed mild esophagitis in 10% of the patients with successful eradication, while no patient with failed eradication showed this alteration. However, the comparison between these results did not reach statistical significance. The hypothesis that *H pylori* eradication increases the chances of developing reflux disease is still a matter of debate[19]. The studies which followed the observations of Labenz *et al*[20], that duodenal ulcer patients were more likely to develop endoscopic esophagitis after *H pylori* eradication presented controversial results. A few authors[21,22] reported a greater incidence of esophagitis in patients with cure of the infection, while other studies failed to confirm these observations[23].

In conclusion, 1-wk treatment with RBC-clarithromycin has shown to be a safe and well tolerated therapy for eradication of *H pylori*, achieving a satisfactory rate of eradication of the infection, comparable to that observed with the 2-wk regimen of the therapy. Triple therapy is currently recommended as the first line treatment, especially in developed countries. The potential benefits of the 1-wk dual therapy, such as lower cost, simplicity of using and low incidence of side effects, associated to its reasonable eradication rates, indicate that this may be an effective alternative for the eradication of *H pylori* infection in developing countries.

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