



Bismuth quadruple therapy versus levofloxacin triple therapy for first-line *helicobacter pylori* eradication treatment: multicenter study

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General Note



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ABSTRACT

Background: Bismuth-containing quadruple regimen and levofloxacin-based triple therapy are recommended as first-line therapy in areas with high clarithromycin and metronidazole resistance. However, increasing resistance to levofloxacin in Vietnam can affect the

success rate of levofloxacin-based triple therapy. There have been few studies comparing the efficacy of bismuth-based quadruple therapy with levofloxacin-based triple therapy for the first-line treatment of *H. pylori* infection in our country. **Patients and Methods:** We included 658 patients with *H. pylori* infection. However, there were 167 patients lost to follow-up. Four hundred ninety-one patients were randomly assigned either to the bismuth-containing quadruple regimen (Group RBMT, N=252) or to levofloxacin triple (Group RAL, N=239). Both groups treated for 14 days. Eradication of *H. pylori* was assessed by 13C- urea breath test or Closet 4-8 weeks after therapy. **Results:** The *H. pylori* eradication rates of Group RBMT and Group RAL on the intention to treat analysis (ITT) were 84.1% in Group RBMT and 77.4% in Group RAL ($P<0.05$). The per-protocol eradication rates were 95.9% and 80.1%, respectively ($p<0.05$). Side effects were significantly higher in the Group RBMT 73.3% than Group RAL 36.4% ($p<0.05$). The compliance rate of more than 90% of Group RBMT and Group RAL were 78.6% and 88.3% ($p<0.05$), respectively. **Conclusions:** A 14-day course of levofloxacin triple therapy appeared to be more productive and better tolerated than a 10-day bismuth-based quadruple therapy in the treatment of persistent *H. pylori* infection. However, the bismuth-containing quadruple regimen had more adverse effects and lower medication adherence than that of levofloxacin-based triple therapy.

Keywords: Bismuth-containing quadruple regimen, levofloxacin-based triple therapy, *Helicobacter pylori* infection

1. INTRODUCTION

Helicobacter pylori infection (*H. pylori*) is one of the most common infections. *H. pylori* infection is a major cause of gastritis, stomach and duodenal ulcers, and stomach cancer. *H. pylori* eradication treatment improves gastritis, promotes healing of ulcers, and reduces the incidence of gastric cancer. *H. pylori* eradication is becoming more difficult due to increased antibiotic resistance. According to the Maastricht IV / Florence consensus (Malfertheiner, 2017), for areas with clarithromycin and metronidazole resistance rates higher than 15% as in our country, a four-drug treatment with Bismuth for 14 days is recommended as a regimen. The first choice for untreated *H. Pylori* infected patients.

Levofloxacin triple therapy is also considered the first choice of treatment according to the guidelines of the American College of Gastroenterology (ACG) 2017 and according to Maastricht IV / Florence in the absence of Bismuth, this regimen was replaced. However, in our country, levofloxacin resistance up to 41.3% (Phan et al., 2015) affects the efficacy of levofloxacin 3-drug regimens. Because the levofloxacin 3-drug regimen has fewer side effects and is more straight forward than the 4-pill regimen containing Bismuth, this regimen is more often prescribed to *H. pylori* infected patients.

2. MATERIALS AND METHODS

Conduct randomized, multicenter studies. Patients diagnosed with *H. pylori* infection indicated for treatment at the gastroenterology clinic of Ho Chi Minh City University of Medicine and Pharmacy, and Dai Phuoc City Clinic, HCM and Thong Nhat hospital. Patients aged 18 and older diagnosed with *H. pylori* infection indicated for treatment at the gastroenterology clinic of Ho Chi Minh City University of Medicine and Pharmacy. Patients are diagnosed with *H. pylori* infection when they meet at least one of the following criteria: 1) Positive urease test (CLO test) positive; 2) Positive C13 (C13 urea-breath test).

Indications for treatment of *H. pylori*: 1) Stomach / duodenal ulcer diagnosed by upper gastrointestinal endoscopy; 2) Functional dyspepsia as standard ROME IV-2016.

Patients with *H. pylori* infection who met the study criteria were randomized to receive one of the following two regimens (Figure 1):

Regimen 1: 4 drugs with Bismuth (RBMT group) with the time and dosage recommended by Maastricht V (2017) including rabeprazole (Pariet) 20mg x 2 doses 30 to 60 minutes before meals; Colloidal bismuth subcitrate (Trymo120mg) 1 tablet x 4 times daily or Tripotassium dinitrate bismuthate (Ducas 300mg); Tetracycline 500 mg1 tablet x 4 times/day, Metronidazole (Flagyl) 250mg 2 tablets x 3 times/day.

Regimen 2: 3 drugs with levofloxacin (RAL group), including rabeprazole (Pariet) 20mg twice daily before eating 30-60 minutes, levofloxacin (Tavanic) 500mg/day, amoxicillin 1000mg twice /day.

Monitoring and checking for *H. pylori* after treatment: Patients are re-examined after 2-3 weeks to evaluate side effects and adherence. Check *H. pylori* status after 4-8 weeks of treatment with a rapid urease test (CLO test) or C13 breathe test (C13 urea-breath test). The patient did not take any other antibiotic or Bismuth for at least four weeks, proton pumps inhibitor for at least two weeks, and H2 receptor antagonist for at least one week before re-checking for *H. pylori* infection. **Evaluation of adherence:** <50% of oral medication is not compliant, 50- <80% has poorly adherent, ≥80% is adherent. Patients who are ≥80% compliant will be placed in the analysis group according to the study design (PP).

Data processing: by the software of Stata 12, $p < 0.05$ is statistically significant. Use the χ^2 test or calibrate Yate's to compare two ratios. Compare two averages by t-tests.

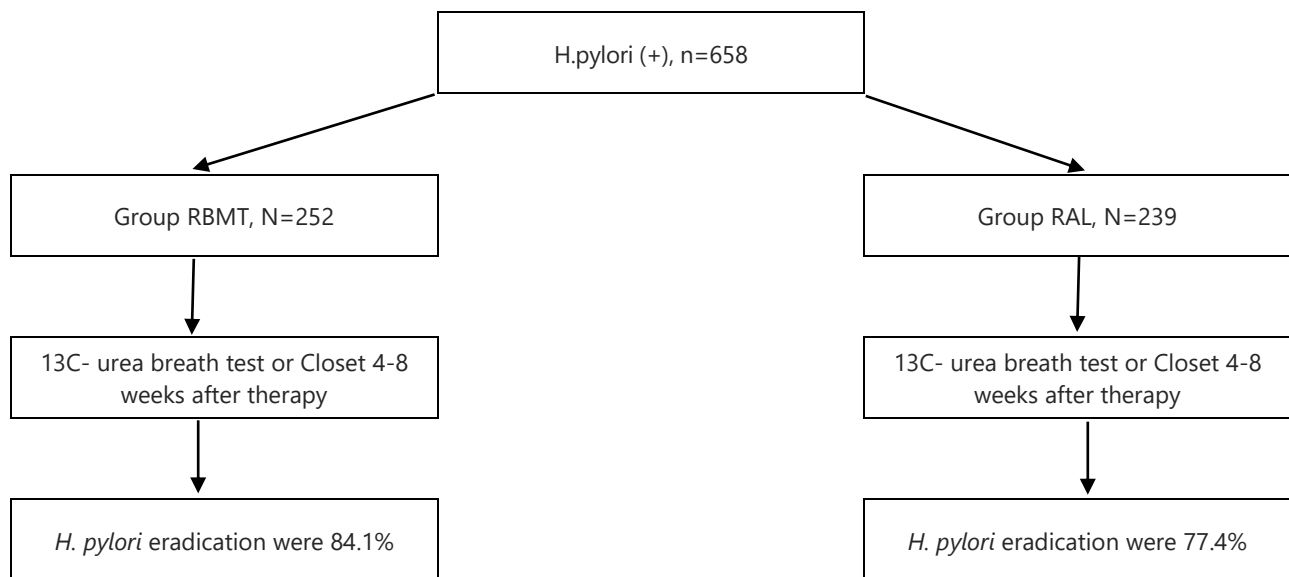


Figure 1 Flow chart of the patients

3. RESULTS

A total of 658 *H. pylori* patients met the criteria, were included in the study conducted at Ho Chi Minh City University of Medicine and Pharmacy, Dai Phuoc City Clinic. Ho Chi Minh City and Thong Nhat Hospital from January 2018 to May 2019. Six hundred fifty-eight patients were randomly divided into two groups, 331 patients treated with a 4-drug regimen with Bismuth (RBMT group), and 327 patients treated according to levofloxacin triple therapy regimen (RAL group). There were 79 patients of the RBMT group, and 88 patients of the RAL group without any follow-up were excluded from the study. RBMT group had 252 patients, of which 19 patients complied with <80% and 12 cases discontinued due to side effects. The RAL group had 239 patients, of which three complied <80% and five discontinued due to side effects. There are differences between the two groups in terms of sex ratio and patients with comorbidities (Table 1). *H. pylori* eradication rate of RBMT group was higher than the RAL group with ITT and PP (Table 2). The proportion of patients with side effects and drug discontinuation due to side effects of the RBMT group was significantly higher than the RAL group (Figure 2). The treatment compliance rate of over 90% of patients for RBMT was significantly lower than the RAL group (Table 3).

Table 1 Features of 2 groups

	Group (RBMT)	Group (RAL)	p
N	252	239	
Male	96/252 (38.1%)	109/239 (45.6%)	<0.05
Age	43.23±12.51	46.23±10.45	>0.05
Ulcers/gastritis	65.5%	72.9%	>0.05
Comorbid disease (HCRKT, GERD)	28.7%	34.4%	<0.05

Table 2 *H. pylori* eradication effect

	Group RBMT	Group RAL	P
ITT	212/252 (84.1%)	185/239 (77.4%)	<0.05
95% CI	80.3 – 94.2	73.6 – 83.5	
PP	212/221 (95.9%)	185/231 (80.1%)	<0.05
95% CI	88.5 – 99.2	76.5 – 88.3	

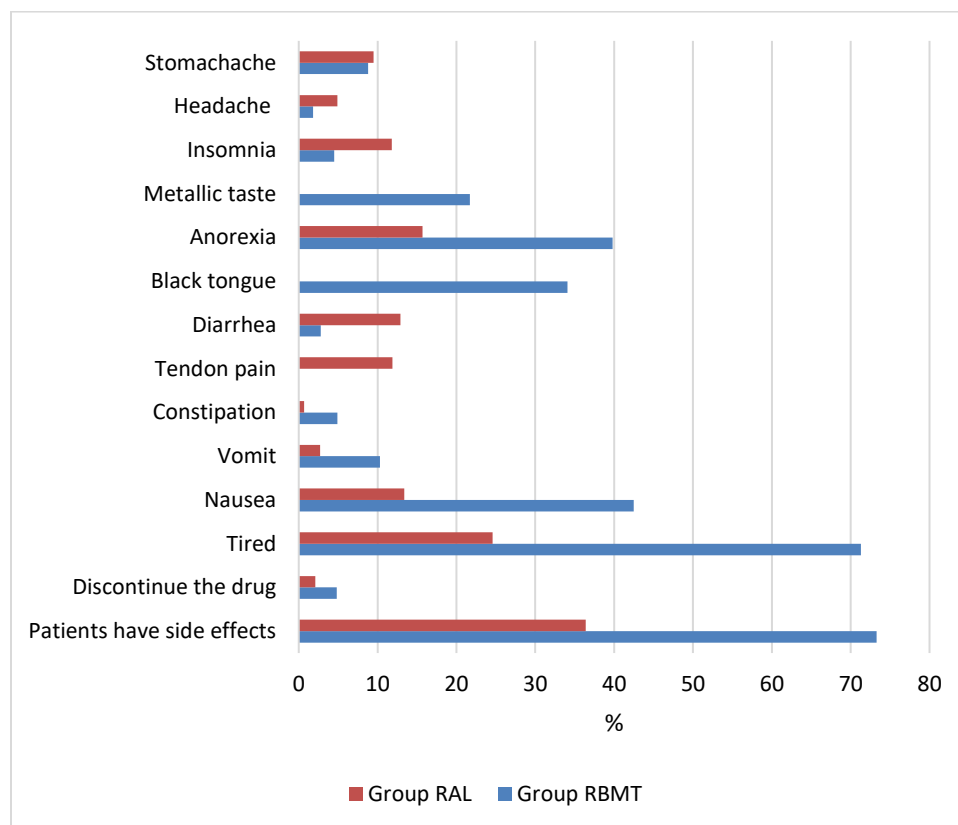


Figure 2 Side effects

Table 3 Compliance to treatment

Compliance level	Group RBMT % (n)	Group RAL % (n)	P
< 80%	19/252 (7.5)	3/239 (1.3)	
≥80%	233/252 (92.5)	236/239 (98.7)	
≥90%	198/252 (78.6)	211/239 (88.3)	<0.05

4. DISCUSSION

Table 1 compares the study population characteristics of 2 groups of RBMT and RAL, showing that the age and % of patients with peptic ulcers with no endoscopy have no significant difference between the two groups. The rates of men and patients with comorbidities such as irritable bowel syndrome (IBS) and gastroesophageal reflux disease (GERD) were significantly different between the two groups. The efficacy of *H. pylori* eradication depends mainly on drug resistance and treatment adherence. The comorbidities may affect adherence and side effects.

The strongest predictor of *H. pylori* treatment failure is antibiotic resistance. In areas with high rates of clarithromycin resistance, a bismuth 4-drug regimen is recommended instead of triple clarithromycin-based regimens. Eradicate *H. pylori*, for the first time. In our study, the RBMT regimen, according to ITT and PP, was 94.7% and 96.8%, similar to the previous research by TTT Tuong (98.3% and 98.1%) (Tuong, 2017). Our research results showed that the *H. pylori* eradication rate for the first time of the 4-drug regimen with Bismuth in 14 days was significantly higher than the 4-drug regimen with Bismuth in 10 days as the research of Dang Ngoc Quy Hueis 79.5% according to ITT and 90.6 according to PP (Hue, 2019). However, the demographic characteristics studied in the study of Dang Ngoc Quy Hue are patients with chronic gastritis and the criteria for successful eradication when all three tests of CLO test, epithelial histology, and trunk histology taste, so the comparison of treatment effects is only of relative value. For international studies, our success eradication rate is similar to that of Sun at 93.7%, according to ITT and 97.4, according to PP. From the study results, we found that the efficacy of *H. pylori* 4-drug regimen with Bismuth-eradication in 14 days was very high for patients who had never been treated in the situation of antibiotic resistance of *H. Pylori* in water. I am now.

Levofloxacin-containing regimens are the first selectable regimen for *H. pylori* eradication, according to the American Gastrointestinal Association (ACG) and Maastricht IV / Florence 2017 (Malfertheiner, 2017). Levofloxacin is a fluoroquinolone

antibiotic with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and atypical respiratory pathogens. Recently, several studies have evaluated the effectiveness of levofloxacin-based therapies in the treatment of *H. pylori* infection. Previous research has shown that a combination of PPI, amoxicillin, and levofloxacin is the leading treatment regimen with high eradication rates of *H. pylori* (about 90%) (Gisbert JP, 2007; Rispo A, 2007). However, in a meta-analysis 2016 study, the efficacy of the regimen for first-time treatment is quite low at 80.7%, especially in areas where the levofloxacin resistance rate is > 5%, the effectiveness drops below 80%.

Our research results show that the removal efficiency of RAL under ITT and PP is quite low, 77.4%, and 80.1%, much lower than the RBMT regimen. With the high resistance of levofloxacin in our country, according to author Phan Nam Trung (2015) (Phan et al., 2015), the primary antigen is 35.6%. The secondary is 63.2%, *H. pylori* eradication rate. The levofloxacin triple therapy regimen of our country is also not high, most of them less than 85% (Trung, 2009; Di, 2011; Thao, 2017).

The majority of patients using the RBMT regimen had side effects of 73.3% lower than that of Dang Ngoc Quy Hue with 81.93% (Hue, 2019). Common side effects of this regimen are fatigue, nausea, black tongue, and loss of appetite. Whereas the levofloxacin triple-drug regimen had significantly fewer side effects, only 36.4% of patients had side effects with the common side effects of fatigue, anorexia, nausea, and insomnia. In the study, the proportion of patients who had to discontinue the drug due to side effects for Bismuth 4-drug regimen (4.8%) was higher than the 3-drug regimen with levofloxacin one patient (2.1%). Fatigue and nausea are the two most common side effects for both regimens. High doses of metronidazole (1500mg) and levofloxacin are common side effects. Overseas studies when using Bismuth 4-drug regimen also show that the rate of severe side effects to discontinue the drug is not high <5% (Liang X, 2013). Careful counseling for patients before treatment on the effectiveness, possible side effects of the regimen, and advising patients to be encouraged in the course of timely therapy when necessary will help patients adhere to proper treatment. In this study, the proportion of patients who adhered to the drug $\geq 90\%$ of the 4-drug regimen with Bismuth was lower than the 3-drug regimen with levofloxacin (78.5% versus 88.3%). The 4-drug regimen with Bismuth has more side effects, and the treatment is more complicated than the 3-drug regimen with levofloxacin, so the proportion of patients who follow treatment is lower.

5. CONCLUSION

The efficacy of *H. pylori* eradication for the first 4-drug regimen with Bismuth is higher than the 3-drug regimen with levofloxacin. However, it is more effective, and the patient's compliance rate is lower than the 3-drug regimen with levofloxacin.

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Conflicts of Interest: The authors declare no conflict of interest.

Informed consent

Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical approval for study protocol

The study was approved by the Medical Ethics Committee of Pham Ngoc Thach University (ethical approval code: 0192-PNTU).

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