

DOI: <http://dx.doi.org/10.18203/2319-2003.ijbcp20203149>

## Original Research Article

# The impact of bismuth adding to rabeprazole, amoxicillin and clarithromycin on eradication rate of *Helicobacter pylori*

Mohammad Sadrkabar<sup>1</sup>, Masoud Tasouji<sup>2</sup>, Afshan Sharghi<sup>3\*</sup>, Abbas Yazdanbod<sup>4</sup>

<sup>1</sup>Department of Internal Medicine, Islamic Azad University, Tabriz Branch, Tabriz, Iran

<sup>2</sup>Faculty of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran

<sup>3</sup>Department of Community Medicine, Faculty of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran

<sup>4</sup>Department of Internal Medicine, Faculty of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran

**Received:** 07 June 2020

**Revised:** 09 July 2020

**Accepted:** 10 July 2020

### \*Correspondence:

Dr. Afshan Sharghi,

Email: [afshan.sharghi@arums.ac.ir](mailto:afshan.sharghi@arums.ac.ir)

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

## ABSTRACT

**Background:** High prevalence of *Helicobacter pylori* infection and induction of resistance as a result of consumption of antibiotics necessitates an ongoing effort for evaluation of new regimen to overcome this phenomenon. Intensive efforts are being made to identify such an optimal regimen, but there are many obstacles hindering the achievement of this goal. This study aimed to investigate the impact of adding bismuth to rabeprazole, amoxicillin and clarithromycin on rate of *H. pylori* eradication.

**Methods:** In this randomized clinical trial, 60 patients with dyspepsia and positive gastric biopsy for *H. pylori* in endoscopy were recruited. The first group (A) received rabeprazole for 6 weeks, amoxicillin and clarithromycin for 2 weeks either with bismuth for 2 weeks and the second group (B) received rabeprazole for 6 weeks, amoxicillin and clarithromycin for 2 weeks either without bismuth. Four weeks after the treatment, the compliance and eradication were evaluated using stool antigen of helicobacter. The patients who could complete the therapeutic regimen were assigned for analysis.

**Results:** *H. pylori* eradication rates were 70% and 56.6% in two groups A and B (with and without Bismuth), respectively and the difference was significant. There is a significant relationship between the studied groups and the results of fecal antigen of *H. pylori*.

**Conclusions:** The bismuth had a significant effect on the success of eradication rate of *H. pylori* and its impact adding to the treatment regimen containing clarithromycin was effective on eradication success rate.

**Keywords:** *Helicobacter pylori*, Eradication, Treatment regimens

## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is a gram-negative bacterium found on the luminal surface of the gastric epithelium. The bacterium induces chronic inflammation of the underlying mucosa and typically infects the stomach in the first few years of life. It was isolated for the first time by Marshall and Warren.<sup>1-3</sup> It survives in the acidic environment of the gastric mucosa and causes

gastritis, peptic ulcers, mucosa-associated lymphoid tissue lymphoma, and gastric cancer. Therefore, the eradication of *H. pylori* can markedly lower gastric and duodenal ulcer recurrence and allowing the treatment of mucosa-associated lymphoid tissue lymphoma.<sup>2-5</sup>

*H. pylori* treatment continues to be a challenge for physicians as antimicrobial resistance has continued to increase worldwide in part due to overuse of antibiotics

in medicine and agriculture.<sup>6</sup> While many international guidelines still recommend standard triple therapy as a first line therapy, they often include a caveat about the problem of increasing clarithromycin resistance. Several recent large clinical trials and meta-analyses have shown that the eradication rate of standard triple therapy has generally declined to unacceptable levels (i.e., 80% or less) with some European studies reporting failure rates of 25-60%.<sup>5-7</sup> Several strategies including bismuth-containing and non-bismuth-containing quadruple therapies (including sequential, concomitant and hybrid therapies) have been shown to produce acceptable cure rates in the presence of clarithromycin resistance.<sup>8-10</sup>

The first-line choice of treatment for *H. pylori* infection in the United States and Europe consists of a conventional triple therapy, in which a proton pump inhibitor (PPI), clarithromycin, and amoxicillin are administered for 7-14 days.<sup>4-6</sup> Conventional triple therapy is also recommended as a first-line therapy by Asian-Pacific and Brazilian consensus groups.<sup>7,8</sup> However, over the past few years, the efficacy of conventional triple therapy has decreased, with eradication rates of <80%, especially in the region with high clarithromycin resistance, including Turkey. Decreased eradication rates are due primarily to increased bacterial resistance to clarithromycin, indicating the need for new first-line treatments.<sup>11-14</sup>

Bismuth is cytoprotective and antibacterial agent which has been safely used for three centuries. The addition of bismuth compounds to different antibiotic combinations have been reported to provide a favorable effect on eradication rates.<sup>15-19</sup>

This study aimed to investigate the impact of adding bismuth to rabeprazole, amoxicillin and clarithromycin on rate of helicobacter pylori eradication.

## METHODS

### *Study design and patients*

From October 2016 to 2017, this study was undertaken at Imam Khomeini Hospital of Ardabil city. The study subjects were patients with gastric symptoms (dyspepsia) and confirmed gastritis, with gastric and duodenal ulcers on esophagogastroduodenoscopy and *H. pylori* infection was diagnosed through histologic examination (Giemsa stain) of antral and body biopsy samples diagnosed histopathologically documented *H. pylori* infection. Patients were considered infected by *H. pylori* if resulted positive.

The subjects were randomly divided into two groups using a random number. The first group was treated with Rabeprazole 20 mg (b.i.d, 30 minutes before meals) for six weeks, amoxicillin 1000 mg (b.i.d, an hour after meals), bismuth sub-citrate 300 mg (equivalent to Bi<sub>2</sub>O<sub>3</sub> 120 mg; two swallowed tablets, an hour before breakfast

and dinner) and clarithromycin 500 mg (b.i.d, an hour after meals) for two weeks (30 patients). The second group was treated with rabeprazole for 6 weeks, amoxicillin and clarithromycin for 2 weeks (30 patients). Four weeks after the treatment period, we confirmed *H. pylori* eradication using fecal antigen of the *H. pylori*.

### *Data collection*

Data collected by a checklist included demographic information, history of smoking, alcohol consumption, previous upper gastrointestinal bleeding and endoscopic findings including, gastritis, erosions, and the presence or absence of bulbar deformity.

### *Stool antigen test (SAT)*

The stool samples were tested for the presence of *H. pylori* antigen with ELISA method (DIA.PRO, diagnostic Bioprobes, Italy) according to the recommendations of the manufacturer.

### *Inclusion and exclusion criteria*

Patients with dyspepsia and positive gastric biopsy for *Helicobacter pylori* in endoscopy were recruited in the study and patients with previous attempt of *H. pylori* eradication therapy; recent use of antibiotic or bismuth salts or proton-pump inhibitors in the last 2 months before the study, chronic use of nonsteroidal anti-inflammatory drugs or corticosteroids, severe comorbid diseases, gastric malignancy including adenocarcinoma and lymphoma; pregnancy or lactation, diarrhea, prior gastric surgery, allergy to any of the drugs in the current treatment; age under 18 years, were excluded from the study.

### *Statistical analysis*

Data analysis was performed using statistical software package program (SPSS) version 22.0 (IBM, USA). The normality of data was checked by K-S test and results showed that the distribution of data was normal and we used parametric tests for analysis data. Inter group comparisons of categorical variables were done using Chi-square test and continuous variables were compared using student's t-test. Categorical variables were presented as percentages or counts and continuous variables were presented as mean and standard deviation in descriptive analysis. Results were evaluated at 95% of confidence interval (CI), and significance was evaluated for each parameter at p<0.05.

### *Ethical approval*

The result of this study was approved by Ardabil University ethical committee and registered by code IR-ARUMS-REC 1396-85. Also, this study registered in IRCT with code IRCT2017111827097N2. Informed

consent was obtained from each patient before enrolling into the study.

**RESULTS**

**Patient characteristics**

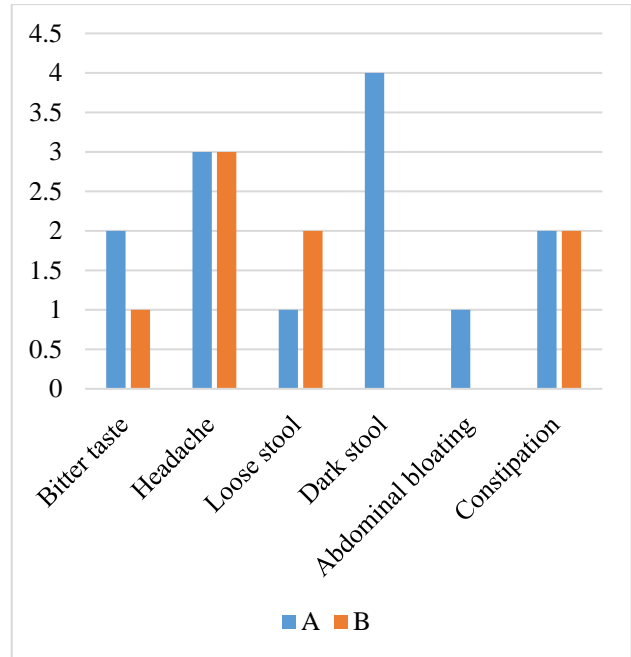
A total of 60 patients were included. Table 1 shows baseline characteristics of two groups. Groups did not differ with regard to demographical and clinical characteristics. There was no difference (p=0.8) between the average ages of the groups, which were 51.24±11.87 (18-66) and 49.7±13.01 (25-75) years in the A and B groups, respectively. The male ratios were 36.66 and 43.3 (p=0.9), respectively. Two groups were matched approximately in term of age, education, job and gender and the difference between two groups were not significant.

**Treatment success**

In the analysis, the successful eradication rate in the patients who experienced successful was 70% in the A group (95% CI: 0.57-0.72) and for patients in the B group was 56.66% (95% CI: 0.61-0.86). There was significant difference in eradication rate among the two groups (p=0.005) (Table 2).

**Adverse drug reaction**

Of all patients, 21 (35%) reported minor adverse drug reactions. The percentages of patients with adverse reactions in the A group with 43.3% (13/30) was significantly more than B group with 26.6% (8/30) (p=0.03).



**Figure 1: The frequency of adverse drug reactions in all samples.**

In order of frequency, bitter taste, loose stool, headache, dark stool, and abdominal bloating were the most common adverse reactions in all study group. Dark stool, abdominal bloating, and headache were the most common adverse reactions in the A group. Bitter taste, headache, and loose stool were the most common events in the sequential group and in the B group. However, these developments were not statistically significant, and there were no major adverse reactions (Figure 1).

**Table 1: Characteristics of patients' N (%).**

Characteristics	Group A	Group B	P value
<b>Age (years)</b>	51.24±11.87	49.7±13.01	P=0.8
<b>Gender</b>	Male	11 (36.6)	P=0.7
	Female	19 (63.3)	
<b>Education</b>	Illiterate	6 (20)	0.42
	Under graduated	21 (70)	
	Graduated	3 (10)	
<b>Job</b>	Non-employee	26 (86.7)	0.36
	Employee	4 (3.3)	

**Table 2: Eradication rates of H. pylori in two groups.**

Groups	Patients (n)	Eradication rate (%)	P value
<b>A</b>	21/30	70	p=0.007
<b>B</b>	17/30	56.6	

## DISCUSSION

The major factor affecting the success rate of *H. pylori* eradication is resistance to antibiotics. Resistance rate for clarithromycin has been reported as 8-30% and for metronidazole as 15-66% in the world.<sup>10</sup> Amoxicillin resistance has been reported as under 1%. Since the presence of dual resistance theoretically removes both clarithromycin and metronidazole leaving only the PPI and amoxicillin dual regimen. Fourteen days dual therapy with standard dose PPI provides approximately 50% of treatment success and approximately one-half that at 7 days. Therefore, Sequential therapy ST (amoxicillin 1 g plus a PPI b.i.d. for 5 days, then clarithromycin 500 mg and tinidazole or metronidazole 500 mg b.i.d plus a PPI b.i.d for remaining 5 days) is likely to be an unacceptable choice in regions where both clarithromycin and metronidazole resistance are common. Recently, in our region, metronidazole resistance was reported to be more than 40% and clarithromycin resistance was reported to be more than 30%. So that ST is also not suitable treatment protocol for our region. Previous studies from our country are in accordance with our results.<sup>10,20</sup>

There is growing data about useful effects of bismuth compounds in *H. pylori* eradication treatment. Bismuth containing quadruple treatment has been showed to provide better eradication rates comparing to standard triple treatment, and it has been recommended as a first-line treatment in regions which have high clarithromycin rates.<sup>9</sup>

As previously mentioned, the use of standard triple therapy is not satisfactory for achieving a low eradication rate, although the efficacy of this therapy has been improved with the addition of bismuth. Xu et al reported that 7 days of standard triple therapy plus bismuth increased the eradication rate from 66.67% to 82.09% according to ITT analysis.<sup>20</sup> When the treatment was extended to 14 days, the ITT eradication rate reached 93.7% compared with 80.0% after 7 days of treatment, which suggested that the addition of bismuth can overcome *H. pylori* resistance to clarithromycin.<sup>21</sup>

Although, bismuth-containing groups is a highly effective regimen that could be recommended as a first-line therapy, bismuth is not available in many developed countries due to its potential nephrotoxicity.<sup>22-24</sup> However, the results of a meta-analysis that included 35 randomized controlled trials involving 4763 patients detected no statistically significant difference in the total number of adverse events after the use of bismuth. Bismuth is safe and well-tolerated for the treatment of *H. pylori*. Moreover, with the availability of new single (three in one) capsule-containing bismuth substrate, metronidazole, and tetracycline, the number of tablets needs to be taken in the bismuth quadruple group will be substantially decreased and this will also likely increase drug compliance.<sup>25</sup> The only adverse event that occurred with significant frequency was dark stools.<sup>26</sup> In this

study, the most adverse reaction of bismuth-containing groups was the dark stool, too. Clinicians should, however, avoid the prescription of bismuth as a gastric mucosa protectant for long-term use. ST has been reported to be more effective than standard triple therapy in many Asian countries. There was a difference among the eradication rates of ST in several countries, with 95%, in Thailand; and 89%, in China.<sup>23,24</sup> One of these studies from our country which is conducted by Ergul et al have reported high eradication rates 90.7% with the addition of bismuth to the standard triple regimen. However, they had not compared the same regimen without bismuth simultaneously.<sup>22</sup>

Besides the PPI-based treatments which contain PPI, amoxicillin, clarithromycin and bismuth, ranitidine bismuth-based treatments which contain ranitidine bismuth, amoxicillin, and clarithromycin have been also reported not to provide sufficient success.<sup>23,24</sup> Administration time of drugs is a very important factor, which influence the effectiveness. Bismuth has been reported to facilitate the passage of the antibiotic into the microorganism. Coadministration of bismuth compounds with antibiotics has been demonstrated to reduce antibiotic resistance or increase the eradication rates of antibiotic resistant strains.<sup>27</sup> In an in vitro study, bismuth has been found to act as synergistic effect with metronidazole and clarithromycin against antibiotic resistant *H. pylori* strains in agar dilution or E-test methodology using time-kill method.<sup>26</sup> A simple addition of bismuth compound to an antibiotic has been suggested not to overcome the established antibiotic resistance.<sup>26-28</sup> However in the most applications, using of bismuth has been recommended before meal because of it acts at low pH and using of antibiotics have been recommended after meal because of their dyspeptic side effects. We also recommended our patients to use bismuth before meal. Since coadministration is more effective than simple addition, we may fail to demonstrate the real effect of bismuth.

## CONCLUSION

The results of this study showed that the eradication rate of *H. pylori* in group A was significantly more than group B. So, we could result that adding bismuth to rabeprazole, amoxicillin and clarithromycin could be effective on *H. pylori* eradication rate. So, this therapeutic method could be recommended in future.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

## REFERENCES

1. Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. Harrison's Principles of Internal Medicine. Mc Graw Hill; 2015.



2. Rimbara E, Fischbach LA, Graham DY. Optimal therapy for *Helicobacter pylori* infections. Nat Rev Gastroenterol Hepatol. 2011;8:79-88.
3. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, et al. European Helicobacter Study Group. Management of *Helicobacter pylori* infection - the Maastricht IV/Florence Consensus Report. Gut. 2012;61:646-64.
4. Chey WD, Wong BC. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. Am J Gastroenterol. 2007;102:1808-25.
5. Graham DY, Shiotani A. New concepts of resistance in the treatment of *Helicobacter pylori* infections. Nat Clin Pract Gastroenterol Hepatol. 2008;5:321-31.
6. Gumurdulu Y, Serin E, Ozer B, Kayaselcuk F, Ozsahin K, Cosar AM, et al. Low eradication rate of *Helicobacter pylori* with triple 7-14 days and quadruple therapy in Turkey. World J Gastroenterol. 2004;10:668-71.
7. Francesco DV, Margiotta M, Zullo A, Hassan C, Giorgio F, Burattini O, et al. Prevalence of primary clarithromycin resistance in *Helicobacter pylori* strains over a 15 years period in Italy. J Anti-microb Chemother. 2007;59:783-5.
8. Zullo A, Francesco DV, Hassan C, Morini S, Vaira D. The sequential therapy regimen for *Helicobacter pylori* eradication: a pooled-data analysis. Gut. 2007;56:1353-7.
9. Essa AS, Kramer JR, Graham DY, Treiber G. Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing "concomitant therapy" versus triple therapy for *Helicobacter pylori* eradication. Helicobacter. 2009;14:109-18.
10. Hsu PI, Kao SS. Therapy of *Helicobacter pylori* Infection: Many Drugs for Which Association? In: Manfredi M, de'Angelis GL, editors. *Helicobacter pylori*. New York: Nova Science Publishers, Inc.; 2013: 347-362.
11. Jodlowski TZ, Lam S, Ashby CR. Emerging therapies for the treatment of *Helicobacter pylori* infections. Ann Pharmacother. 2008;42(11):1621-39.
12. Dib J, Alvarez B, Mendez L, Cruz ME. Efficacy of PPI, levofloxacin and amoxicillin in the eradication of *Helicobacter pylori* compared to conventional triple therapy at a Venezuelan hospital. Arab J Gastroenterol. 2013;14(3):123-5.
13. Cho DK, Park SY, Kee WJ, Lee JH, Ki HS, Yoon KW, et al. The trend of eradication rate of *Helicobacter pylori* infection and clinical factors that affect the eradication of first-line therapy. Korean J Gastroenterol. 2010;55(6):368-75.
14. Nadir I, Yonem O, Ozin Y, Kilic ZM, Sezgin O. Comparison of two different treatment protocols in *Helicobacter pylori* eradication. South Med J. 2011;104(2):102-5.
15. Ciccaglione AF, Cellini L, Grossi L, Marzio L. Quadruple therapy with moxifloxacin and bismuth for first-line treatment of *Helicobacter pylori*. World J Gastroenterol. 2012;18:4386-90.
16. Ergul B, Dogan Z, Sarikaya M, Filik L. The efficacy of two weeks quadruple first-line therapy with bismuth, lansoprazole, amoxicillin, clarithromycin on *Helicobacter pylori* eradication: a prospective study. Helicobacter. 2013;18(6):454-8.
17. Xu MH, Zhang GY, Li CJ. Efficacy of bismuth-based quadruple therapy as first-line treatment for *Helicobacter pylori* infection. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2011;40:327-31.
18. Holmes RS, Vaughan TL. Epidemiology and pathogenesis of esophageal cancer. Semin Radiat Oncol. 2007;17(1):2-9.
19. Islami F, Kamangar F. *Helicobacter pylori* and Esophageal Cancer Risk: a meta-analysis. Cancer Prev Res. 2008;42(4):33-8.
20. Xu MH, Zhang GY, Li CJ. Efficacy of bismuth-based quadruple therapy as first-line treatment for *Helicobacter pylori* infection. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2011;40(3):327-31.
21. Sun Q, Liang X, Zheng Q, Liu W, Xiao S, Gu W, et al. High efficacy of 14 days triple therapy-based, bismuth-containing quadruple therapy for initial *Helicobacter pylori* eradication. Helicobacter. 2010;15(3):233-8.
22. Ergul B, Dogan Z, Sarikaya M, Filik L. The efficacy of two weeks quadruple first-line therapy with bismuth, lansoprazole, amoxicillin, clarithromycin on *Helicobacter pylori* eradication: a prospective study. Helicobacter. 2013;18(6):454-8.
23. Ciccaglione AF, Cellini L, Grossi L, Manzoli L, Marzio L. A Triple and Quadruple Therapy with Doxycycline and Bismuth for First-Line Treatment of *Helicobacter pylori* Infection: A Pilot Study. Helicobacter. 2015;20(5):390-6.
24. Ghotaslou R. Prevalence of antibiotic resistance in *Helicobacter pylori*: a recent literature review. World J Methodology. 2015;5(3):164-75.
25. Malfertheiner P, Bazzoli F, Delchier JC, Celinski K, Giguere M, Riviere M, et al. *Helicobacter pylori* eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. Lancet. 2011;377(9769):905-13.
26. Ji R, Li YQ. Diagnosing *Helicobacter pylori* infection in vivo by novel endoscopic techniques. World J Gastroenterology. 2014;20(28):9314-20.
27. Hsu PI, Lin PC, Graham DY. Hybrid therapy for *Helicobacter pylori* infection: a systemic review and meta-analysis. World J Gastroenterology. 2015;21(45):12954-62.
28. Federico A, Gravina AG, Miranda A, Loguercio C, Romano M. Eradication of *Helicobacter pylori* infection: Which regimen first. World J Gastroenterol. 2014;20(3):665-72.

**Cite this article as:** Sadrkabir M, Tasouji M, Sharghi A, Yazdanbod A. The impact of bismuth adding to rabeprazole, amoxicillin and clarithromycin on eradication rate of *Helicobacter pylori*. Int J Basic Clin Pharmacol 2020;9:1280-4.