**Name of Journal: *World Journal of Gastroenterology***

**ESPS Manuscript NO: 30795**

**Manuscript Type: ORIGINAL ARTICLE**

***Retrospective Study***

**Second-line bismuth-containing quadruple therapy for *Helicobacter pylori* eradication and impact of diabetes**

Kim SE *et al.* Bismuth-containing quadruple therapy and diabetes

Sung Eun Kim,Moo In Park, Seun Ja Park, Won Moon, Jae Hyun Kim, Kyoungwon Jung, Hae Koo Kim, Young Dal Lee

**Sung Eun Kim,Moo In Park, Seun Ja Park, Won Moon, Jae Hyun Kim, Kyoungwon Jung, Hae Koo Kim, Young Dal Lee,** Department of Internal Medicine, Kosin University College of Medicine, Busan 49267, South Korea

**Author contributions:** Kim SE interpreted and analyzed the data and wrote the manuscript; Park MI designed, organized, and supervised writing of the manuscript; Park SJ and Moon W helped with data interpretation that was used in the current study; Kim JH and Jung K provided input and organized the data for statistical analysis; Kim HK and Lee YD helped with data analysis; all authors approved the final version of the manuscript.

**Institutional review board statement:** The study was reviewed and approved by the Kosin University Gospel Hospital Institutional Review Board (IRB file No. 2015-03-018).

**Conflict-of-interest statement:** We have no conflicts of interest regarding the current paper.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Correspondence to: Moo In Park, MD, Professor,** Department of Internal Medicine, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, South Korea. mipark@kosinmed.or.kr

**Telephone:** +82-51-9906719

**Fax:** +82-51-9905055

**Received:** October 17, 2016

**Peer-review started:** October 18, 2016

**First decision:** October 28, 2016

**Revised:** November 21, 2016

**Accepted:** January 18, 2017

**Article in press:**

**Published online:**

**Abstract**

***AIM***

To investigate *Helicobacter pylori* (*H. pylori*)eradication rates using second-line bismuth-containing quadruple therapy and to identify predictors of eradication failure.

***METHODS***

This study included 636 patients who failed first-line triple therapy and received 7 days of bismuth-containing quadruple therapy between January 2005 and December 2015. We retrospectively demonstrated *H. pylori* eradication rates with respect to the year of therapy as well as demographic and clinical factors. *H. pylori* eradication was confirmed by a 13C-urea breath test or a rapid urease test at least 4 wk after the completion of bismuth-based quadruple therapy: proton pump inhibitor, metronidazole, bismuth, and tetracycline.

***RESULTS***

The overall eradication rates by intention-to-treat analysis and per-protocol analysis were 73.9% (95%CI: 70.1%-77.4%) and 94.5% (95%CI: 92.4%-96.5%), respectively. Annual eradication rates from 2005 to 2015 were 100.0%, 92.9%, 100.0%, 100.0%, 100.0%, 97.4%, 100.0%, 93.8%, 84.4%, 98.9%, and 92.5%, respectively, by per-protocol analysis. A multivariate analysis showed that diabetes mellitus (OR = 3.99; 95%CI: 1.56-10.20, *P* = 0.004) was associated with *H. pylori* eradication therapy failure.

***CONCLUSION***

The second-line bismuth-containing quadruple therapy for *H. pylori* infection is still effective in Korea, and diabetes mellitus is suggested to be a risk factor for eradication failure.

**Key word:** *Helicobacter pylori*; Disease eradication; Treatment failure; Bismuth; Diabetes mellitus

**© The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** This study investigated the efficacy of 7 d of second-line bismuth-containing quadruple therapy for *Helicobacter pylori* *(H. pylori)* infection and identified risk factors for eradication failure in South Korea. The overall eradication rate per-protocol analysis was 94.5% in the current study. Additionally, diabetes mellitus was related to *H. pylori* eradication therapy failure. Therefore, second-line bismuth-containing quadruple therapy for *H. pylori* infection is still worth considering in South Korea, and diabetes mellitus is suggested to be a risk factor for eradication failure.

Kim SE,Park MI, Park SJ, Moon W, Kim JH, Jung K, Kim HK, Lee YD. Second-line bismuth-containing quadruple therapy for *Helicobacter pylori* eradication and impact of diabetes. *World J Gastroenterol* 2017; In press

**INTRODUCTION**

*Helicobacter pylori (H. pylori)* is a global pathogen that causes gastritis, peptic ulcers, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer[[1](#_ENREF_1)]. The International Agency for Research on Cancer, a branch of the World Health Organization, has declared that *H. pylori* is a definite gastric carcinogen (group I)[[2](#_ENREF_2),[3](#_ENREF_3)]. Therefore, *H. pylori* eradication is crucial to maintain public health, especially in high *H. pylori* and gastric cancer prevalence areas.

Various combination therapies are recommended for *H. pylori* eradication due to a decrease in eradication rates. According to the Maastricht IV/Florence consensus report, clarithromycin-containing therapy (comprised of a proton pump inhibitor (PPI), amoxicillin, and clarithromycin) is recommended for first-line eradication treatment, and bismuth-containing quadruple therapy (comprised of a PPI, metronidazole, bismuth, and tetracycline) is recommended for second-line eradication treatment if first-line eradication therapy fails[[4](#_ENREF_4)]. Guidelines for the treatment of *H. pylori* infection in South Korea are similar to recommendations in the Maastricht IV/Florence consensus report. Specifically, clarithromycin-containing triple therapy is the recommended first-line eradication therapy, and bismuth-containing quadruple therapy is recommended for the second-line eradication treatment if the clarithromycin-based triple therapy fails[[5](#_ENREF_5)].

In general, clarithromycin-containing therapy is recommended for first-line eradication treatment in low (< 20%) clarithromycin resistance areas[4]. However, the eradication rates for clarithromycin-containing triple therapy have been decreasing significantly in Korea in recent years due to increased *H. pylori* antibiotic resistance[[6](#_ENREF_6),[7](#_ENREF_7)]. In addition, there is controversy about the role of bismuth-containing quadruple therapy as a second-line therapy for *H. pylori* eradication due to a decrease in eradication rates for bismuth-containing quadruple therapy in Korea[[8](#_ENREF_8),[9](#_ENREF_9)].

The aims of the present study were to identify the effects of second-line eradication therapy using bismuth-containing quadruple therapy at a single center over the past 11 years, and to evaluate risk factors associated with the failure of second-line eradication therapy.

**MATERIALS AND METHODS**

***Study population***

Patients who failed clarithromycin-containing triple therapy and received second-line bismuth-containing quadruple therapy at Kosin University Gospel Hospital from January 2005 to December 2015 were retrospectively enrolled in this study. *H. pylori* positivity was identified using a 13C-urea breath test or a rapid urease test before and after eradication therapy. Patients lost to follow-up were defined as patients who received the second-line bismuth-containing quadruple therapy with unknown results regarding eradication success or failure. Compliance was classified as good or poor by pill count in the medical records. Patients who took 80% or more of the prescribed medicine were included in the good compliance group, and those who took less than 80% of the prescribed medicine were placed in the poor compliance group.

We investigated demographic features: area of residence, smoking and alcohol habits, diabetes mellitus, hypertension, endoscopic findings, and adverse effects of eradication therapy. Rural or urban residence was regarded as living or not living in the metropolitan cities of Korea, respectively. All patients underwent endoscopy,andendoscopic findings (such as gastric ulcers, duodenal ulcers, gastric and duodenal ulcers, a previous endoscopic submucosal dissection (ESD) state due to adenoma or early gastric cancer (EGC), MALT lymphoma, nodular gastritis, dyspepsia, gastric polyps, and intestinal metaplasia) were identified by endoscopy or by endoscopy with biopsy. Adverse effects after eradication therapy were identified by verification in the medical records. The Institutional Review Board (IRB) of Kosin University Gospel Hospital approved this study (IRB file No. 2015-03-018).

***Helicobacter pylori* *eradication therapy and follow-up***

Patients who failed the first-line clarithromycin-containing triple therapy (standard-dose PPI, 1.0 g amoxicillin, and 0.5 g clarithromycin twice daily for 7 d) were recommended for second-line eradication therapy. The latter was comprised of 20 mg rabeprazole twice daily, 500 mg metronidazole three times daily, 300 mg tripotassium dicitrato bismuthate, and 500 mg tetracycline four times daily for 7 d. Afterwards, a 13C-urea breath test or a rapid urease test was conducted to assess *H. pylori* eradication at least 4 wk after the treatment completion, and at least 2 wk after cessation of PPIs or histamine (H2) receptor antagonists.

***13C-urea breath test***

Patients fasted for at least 4 h before the first breath sample was collected. Then, participants took tablets including 100 mg of 13C-urea (UBiTkitTM, Otsuka Pharmaceutical, Tokyo, Japan) with 100 mL of water orally, and the second breath sample was obtained 20 min after taking the tablets. *H. pylori* infection was analyzed using the 13C-urea breath test (UBiT-IR300®; Otsuka Electronics, Osaka, Japan) on the collected breath samples. The cut-off value in the current procedure was set at 2.5‰.

***Rapid urease test***

To identify *H. pylori* infection with the rapid urease test (CLOtest®; Delta West, Bentley, WA, Australia), an endoscopic biopsy was conducted at the gastric mucosa. The site of gastric mucosal biopsy was antrum and/or corpus, and normal or near-normal gastric mucosa with little atrophy or intestinal metaplasia was removed. The tissue sample was immersed in rapid urea reagent. The result was positive when the reagent color changed from yellow to red at least 12 h later, and the result was negative when there was no change in reagent color.

***Statistical analyses***

All statistical analyses were conducted with the Statistical Package for the Social Sciences software version 20.0 (SPSS, Chicago, IL, United States). The *H. pylori* eradication rate was demonstrated by intention-to-treat (ITT) and per-protocol (PP) analyses. The trend in *H. pylori* eradication rates was analyzed with linear association. Patients lost to follow-up or those with poor compliance were excluded when we performed the PP analysis and univariate and multivariate logistic regression analyses. Categorical variables were analyzed using a Chi-square (*χ2*)-test, and continuous variables were analyzed using the Student’s *t*-test. Univariate and multivariate logistic regression tests were used for the analysis of risk factors, which were expressed as an odds ratio (OR) and 95% confidence intervals (CI). A *P* value < 0.05 was considered statistically significant.

**RESULTS**

***Patient characteristics***

Between January 2005 and December 2015, 636 patients received 7 d of second-line bismuth-containing quadruple therapy after *H. pylori* eradication failure with clarithromycin-based triple therapy. Average age (mean ± standard deviation) was 54.6 ± 11.6 years (range, 17-86 years), and 354 patients (55.7%) were male. Table 1 shows the clinical data and demographic information for enrolled patients. Among 636 patients receiving second-line bismuth-containing quadruple therapy, 138 patients were lost to follow-up, and three patients exhibited poor compliance. Finally, a total of 495 patients were included as subjects for PP analysis and multivariate logistic regression (Figure 1).

***Helicobacter pylori* *eradication rates***

In terms of eradication therapy success or failure, 468 patients achieved successful eradication. The eradication rates by ITT and PP analyses were 73.9% (95%CI: 70.1%-77.4%) and 94.5% (95%CI: 92.4%-96.5%) for second-line quadruple therapy, respectively. Annual eradication rates from 2005 to 2015 were 100.0%, 92.9%, 100.0%, 100.0%, 100.0%, 97.4%, 100.0%, 93.8%, 84.4%, 98.9% and 92.5%, consecutively by PP analysis. The eradication rate for first-line triple therapy decreased over the years (*P* = 0.01). Figure 2 presents the annual eradication rates for the last 11 years.

***Adverse effects of eradication therapy***

Of the 495 patients, 74 patients (14.9%) complained of adverse events after bismuth-based quadruple therapy; fortunately, the adverse events were mild or moderate. Adverse events possibly related to treatment were diarrhea in 16 patients (3.2%), bloating or abdominal pain in 22 patients (4.4%), nausea or vomiting in 26 patients (5.3%), and others (such as myalgia, headache, and bitter sensation in the mouth) in 10 patients (2.0%, Table 2).

***Associated factors for eradication failure***

Associated factors for eradication failure are summarized in Table 3. Univariate and multivariate analyses demonstrated that only diabetes mellitus (OR = 3.99; 95%CI: 1.56-10.20; *P* = 0.004) was significantly related to eradication failure. There was no statistically significant relationship between eradication failure and other factors including age, gender, residence, smoking, alcohol, and hypertension.

**DISCUSSION**

In the current study, the *H. pylori* eradication rate for bismuth-containing quadruple therapy given for 7 d was < 80% by ITT analysis, but was > 90% by PP analysis in patients who failed clarithromycin-containing triple therapy. The frequency of adverse effects was less than 15%, which is consistent with the results of previous studies using bismuth-containing quadruple therapy[[9](#_ENREF_9),[10](#_ENREF_10)].

As a second-line therapy, the effect of bismuth-containing quadruple therapy is controversial. Our PP eradication rate result was consistent with earlier studies, which reported that bismuth-containing quadruple therapy produced a high eradication rate in patients that failed *H. pylori* eradication therapy using clarithromycin-containing triple therapy. A recent multinational study in Europe reported the eradication rates for bismuth-containing quadruple therapy as rescue therapy for 10 d were 93.2%-93.8% by ITT analysis and 94.7%-95.0% by PP analysis[[11](#_ENREF_11)]. Results with bismuth-containing quadruple therapy in China also demonstrated a 10-d bismuth-containing quadruple therapy eradication rate of 88.9% by ITT analysis and 90.9%-91.6% by PP analysis in patients that failed *H. pylori* eradication therapy[[12](#_ENREF_12),[13](#_ENREF_13)]. However, eradication rates using second-line bismuth-containing quadruple therapy revealed diverse results in South Korea. Yoon *et al*[[14](#_ENREF_14)] suggested that a 7-d bismuth-containing quadruple therapy might be as efficient as a 14-d bismuth-containing quadruple therapy for second-line eradication therapy, because a 7-d bismuth-containing quadruple therapy produced 83.5% and 87.7% eradication rates by ITT and PP analyses, respectively, and a 14-d bismuth-containing quadruple therapy produced 87.7% and 88.9% eradication rates by ITT and PP analyses, respectively. In contrast, another study reported that ITT eradication rates for a 7-d bismuth-containing quadruple therapy were 67.4%, and PP eradication rates were 78.2%, whereas ITT eradication rates for a 14-d bismuth-containing quadruple therapy were 72.8%, and PP eradication rates were 84.1%[[9](#_ENREF_9)]. Usually, *H. pylori* eradication rates correlate with patient drug compliance and *H. pylori* antibiotic resistance. Unfortunately, studies to evaluate antibiotic resistance between different areas in South Korea are rare, and one small study determined there was no significant regional difference between *H. pylori* metronidazole and tetracycline resistance inSouthKorea[[15](#_ENREF_15)]. Therefore, the reason for the high PP eradication rate in the current study is unclear. Although regional differences in antibiotic resistance may exist, bismuth-containing quadruple therapy achieved a more than 90% ITT eradication rate in patients who had *H. pylori* resistant to metronidazole (32.7%) and clarithromycin (63.3%)[[11](#_ENREF_11)]. Thus, bismuth-containing quadruple therapy for second-line eradication therapy might even be effective in patients with antibiotic-resistant *H. pylori*.

In terms of adverse effects, most patients in the current study complained of gastrointestinal symptoms including nausea, vomiting, bloating, abdominal pain, or diarrhea. The symptoms were well tolerated, and no serious adverse events were observed. Only one patient wanted to be hospitalized for supportive care due to nausea. With regard to neurologic symptoms, three patients complained of headache or dizziness, but the symptoms were mild. Severe neurological symptoms, such as bismuth-related encephalopathy, were not observed[[11](#_ENREF_11),[16](#_ENREF_16),[17](#_ENREF_17)]. In accordance with previous studies, bismuth-containing therapy for the eradication of *H. pylori* is considered safe and well tolerated[[9](#_ENREF_9),[18](#_ENREF_18)].

Several factors have been postulated as the cause of eradication failure, including age, gender, smoking, alcohol, and specific drug history (*e.g.*, aspirin)[[6](#_ENREF_6),[19-22](#_ENREF_19)]. However, there was no significant relationship between these factors and eradication failure in the current study, except for diabetes mellitus. Diabetes mellitus has been presumed to be a risk factor for *H. pylori* eradication failure based on a recent meta-analysis (RR = 2.19; 95%CI: 1.65-2.90)[[23](#_ENREF_23)]. It is hypothesized that microcirculatory complications related to diabetes mellitus could induce gastroparesis and reduce the absorption of antibiotics into the gastric mucosa, thereby influencing the effect of eradication therapy[[24](#_ENREF_24),[25](#_ENREF_25)]. In addition, drug binding was revealed to be decreased by glycosylation, which was presumed to be associated with levels of blood glucose[[26](#_ENREF_26)]. Concerning antibiotic resistance, the frequent use of antibiotics might increase antibiotic resistance[[23](#_ENREF_23),[27](#_ENREF_27)].A recent Danish nationwide cohort study found that the rates for community-based antibiotic prescriptions were higher in patients with diabetes mellitus compared to the general population[[28](#_ENREF_28)]. Therefore, a more careful choice of *H. pylori* eradication therapy is needed for patients with diabetes mellitus.

Limitations of the present study are that it was performed at a single center and many patients were lost to follow-up, which might have influenced results of the ITT analysis. In addition, antibiotic susceptibility tests were not conducted in this study. Culturing *H. pylori* is difficult, and the response rates for antibiotic susceptibility tests are relatively low. Therefore, this was hard to inspect in all enrolled patients, and there were no standard criteria for identifying antibiotic resistance[9]. Furthermore, we did not diagnose *H. pylori* by histology before and after eradication therapy, as most patients underwent the 13C-urea breath test or the rapid urease test for confirmation of *H. pylori* presence before and after therapy. These limitations could affect the eradication rate. According to the manufacturer, sensitivity and specificity of the rapid urease test were 90% to 95% and 95% to 100%, respectively. A recent meta-analysis reported that sensitivity and specificity of the 13C-urea breath test were 95% to 97% and 91% to 94%, respectively, and that this test only rarely provided false-positive results[[29-32](#_ENREF_29)]. We found that eradication rates based on the 13C-urea breath test and the rapid urease test were 95.1% (327/344) and 93.4% (141/151), respectively (*P* = 0.519). Therefore, there was no significant difference between the two methods. The accuracy of both tests is high and very practical for clinical use[[33](#_ENREF_33)],thus the absence of histology is unlikely to have had a significant effect on this study.

In conclusion, bismuth-containing quadruple therapy might be effective in patients that failed *H. pylori* eradication using clarithromycin-containing triple therapy, and might be worthy of consideration as a useful second-line therapy for *H. pylori* eradication in South Korea. Additionally, patients with diabetes mellitus are at higher risk for eradication failure with bismuth-containing quadruple therapy. Further studies on a larger scale evaluating the effects of second-line bismuth-containing quadruple therapy are needed in the near future in South Korea.

**COMMENTS**

***Background***

*Helicobacter pylori* (*H. pylori*) has been classified as a definite gastric carcinogen (group I) by the International Agency for Research on Cancer. Therefore, *H. pylori* eradication is important to protect public health, especially in areas with high *H. pylori* prevalence. However, the eradication rate for proton pump inhibitor (PPI)-containing triple therapy has decreased worldwide, and an effective rescue treatment is needed.

***Research frontiers***

There is controversy about the role of bismuth-containing quadruple therapy as a second-line therapy for *H. pylori* eradication due to a decrease in eradication rates for bismuth-containing quadruple therapy in South Korea. In addition, risk factors related to the failure of second-line eradication therapy are obscure.

***Innovations and breakthroughs***

This retrospective study was performed to investigate the effects of second-line eradication therapy using bismuth-containing quadruple therapy at a single center over the past 11 years, and to evaluate the risk factors associated with the failure of second-line eradication therapy. According to the high eradication rate and low adverse effects of the therapy, bismuth-containing quadruple therapy is worthy of consideration as a useful second-line therapy for *H. pylori* eradication in South Korea. Additionally, diabetes mellitus is suggested to be a risk factor for eradication failure.

***Applications***

This retrospective study’s design and findings may be helpful for planning further prospective studies on a larger scale which can evaluate the effects of second-line bismuth-containing quadruple therapy and clarify additional risk factors for eradication failure.

***Terminology***

*Helicobacter pylori*:A global pathogen that causes gastritis, peptic ulcers, mucosa-associated lymphoid tissue lymphoma, and gastric cancer. Eradication of *H. pylori* infection is crucial to maintaining public health, especially in high *H. pylori* and gastric cancer prevalence areas.

***Peer-review***

This is a well-designed, although retrospective study including a high number of patients. The methods used are appropriate, the statistics is sound. The difference between ITT and PP eradication rates reflects the real life, while a proportion of patients lost to follow up is high.

**REFERENCES**

1 **Moss SF**, Malfertheiner P. Helicobacter and gastric malignancies. *Helicobacter* 2007; **12 Suppl 1**: 23-30 [PMID: 17727457 DOI: 10.1111/j.1523-5378.2007.00539.x]

2 IARC working group on the evaluation of carcinogenic risks to humans: some industrial chemicals. Lyon, 15-22 February 1994. *IARC Monogr Eval Carcinog Risks Hum* 1994; **60**: 1-560 [PMID: 7869568]

3 **Kim MS**, Kim N, Kim SE, Jo HJ, Shin CM, Lee SH, Park YS, Hwang JH, Kim JW, Jeong SH, Lee DH, Kim JM, Jung HC. Long-term follow-up Helicobacter pylori reinfection rate and its associated factors in Korea. *Helicobacter* 2013; **18**: 135-142 [PMID: 23066652 DOI: 10.1111/hel.12018]

4 **Malfertheiner P**, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]

5 **Kim SG**, Jung HK, Lee HL, Jang JY, Lee H, Kim CG, Shin WG, Shin ES, Lee YC. Guidelines for the diagnosis and treatment of Helicobacter pylori infection in Korea, 2013 revised edition. *J Gastroenterol Hepatol* 2014; **29**: 1371-1386 [PMID: 24758240 DOI: 10.1111/jgh.12607]

6 **Kim SE**, Park MI, Park SJ, Moon W, Choi YJ, Cheon JH, Kwon HJ, Ku KH, Yoo CH, Kim JH, Lee GW, Song SE. Trends in Helicobacter pylori eradication rates by first-line triple therapy and related factors in eradication therapy. *Korean J Intern Med* 2015; **30**: 801-807 [PMID: 26552455 DOI: 10.3904/kjim.2015.30.6.801]

7 **Shin WG**, Lee SW, Baik GH, Huh KC, Lee SI, Chung JW, Jung WT, Park MI, Jung HK, Kim HU, Kim JH, Seol SY, Yoon SM, Jeon SW, Hong SJ, Kim GH, Lee DH, Kim HS, Choi SC, Kang HM, Lee J, Kim JG, Kim JJ. Eradication Rates of Helicobacter pylori in Korea Over the Past 10 years and Correlation of the Amount of Antibiotics Use: Nationwide Survey. *Helicobacter* 2016; **21**: 266-278 [PMID: 26470999 DOI: 10.1111/hel.12279]

8 **Lee BH**, Kim N, Hwang TJ, Lee SH, Park YS, Hwang JH, Kim JW, Jeong SH, Lee DH, Jung HC, Song IS. Bismuth-containing quadruple therapy as second-line treatment for Helicobacter pylori infection: effect of treatment duration and antibiotic resistance on the eradication rate in Korea. *Helicobacter* 2010; **15**: 38-45 [PMID: 20302588 DOI: 10.1111/j.1523-5378.2009.00735.x]

9 **Hwang JJ**, Lee DH, Lee AR, Yoon H, Shin CM, Park YS, Kim N. Fourteen- vs seven-day bismuth-based quadruple therapy for second-line Helicobacter pylori eradication. *World J Gastroenterol* 2015; **21**: 8132-8139 [PMID: 26185386 DOI: 10.3748/wjg.v21.i26.8132]

10 **Lee ST**, Lee DH, Lim JH, Kim N, Park YS, Shin CM, Jo HJ, Song IS. Efficacy of 7-Day and 14-Day Bismuth-Containing Quadruple Therapy and 7-Day and 14-Day Moxifloxacin-Based Triple Therapy as Second-Line Eradication for Helicobacter pylori Infection. *Gut Liver* 2015; **9**: 478-485 [PMID: 25071068 DOI: 10.5009/gnl14020]

11 **Delchier JC**, Malfertheiner P, Thieroff-Ekerdt R. Use of a combination formulation of bismuth, metronidazole and tetracycline with omeprazole as a rescue therapy for eradication of Helicobacter pylori. *Aliment Pharmacol Ther* 2014; **40**: 171-177 [PMID: 24863854 DOI: 10.1111/apt.12808]

12 **Zheng Q**, Dai J, Li X, Lu H, Xiao S. Comparison of the efficacy of pantoprazole-based triple therapy versus quadruple therapy in the treatment of Helicobacter pylori infections: a single-center, randomized, open and parallel-controlled study. *Wei Chang Bing Xue* 2009; **14**: 8-11

13 **Zheng Q**, Chen WJ, Lu H, Sun QJ, Xiao SD. Comparison of the efficacy of triple versus quadruple therapy on the eradication of Helicobacter pylori and antibiotic resistance. *J Dig Dis* 2010; **11**: 313-318 [PMID: 20883428 DOI: 10.1111/j.1751-2980.2010.00457.x]

14 **Yoon JH**, Baik GH, Kim YS, Suk KT, Shin WG, Kim KH, Kim KO, Park CH, Baik IH, Jang HJ, Kim JB, Kae SH, Kim DJ, Kim HY. Comparison of the Eradication Rate between 1- and 2-Week Bismuth-Containing Quadruple Rescue Therapies for Helicobacter pylori Eradication. *Gut Liver* 2012; **6**: 434-439 [PMID: 23170146 DOI: 10.5009/gnl.2012.6.4.434]

15 **Kim JY**, Kim NY, Kim SJ, Baik GH, Kim GH, Kim JM, Nam RH, Kim HB, Lee DH, Jung HC, Song IS. [Regional difference of antibiotic resistance of helicobacter pylori strains in Korea]. *Korean J Gastroenterol* 2011; **57**: 221-229 [PMID: 21519175 DOI: 10.4166/2011.57.4.221]

16 **Tillman LA**, Drake FM, Dixon JS, Wood JR. Review article: safety of bismuth in the treatment of gastrointestinal diseases. *Aliment Pharmacol Ther* 1996; **10**: 459-467 [PMID: 8853750 DOI: 10.1046/j.1365-2036.1996.22163000.x]

17 **Serfontein WJ**, Mekel R. Bismuth toxicity in man II. Review of bismuth blood and urine levels in patients after administration of therapeutic bismuth formulations in relation to the problem of bismuth toxicity in man. *Res Commun Chem Pathol Pharmacol* 1979; **26**: 391-411 [PMID: 392661]

18 **Ford AC**, Malfertheiner P, Giguere M, Santana J, Khan M, Moayyedi P. Adverse events with bismuth salts for Helicobacter pylori eradication: systematic review and meta-analysis. *World J Gastroenterol* 2008; **14**: 7361-7370 [PMID: 19109870 DOI: 10.3748/wjg.14.7361]

19 **Suzuki T**, Matsuo K, Ito H, Sawaki A, Hirose K, Wakai K, Sato S, Nakamura T, Yamao K, Ueda R, Tajima K. Smoking increases the treatment failure for Helicobacter pylori eradication. *Am J Med* 2006; **119**: 217-224 [PMID: 16490464 DOI: 10.1016/j.amjmed.2005.10.003]

20 **Moayyedi P**, Chalmers DM, Axon AT. Patient factors that predict failure of omeprazole, clarithromycin, and tinidazole to eradicate Helicobacter pylori. *J Gastroenterol* 1997; **32**: 24-27 [PMID: 9058291 DOI: 10.1007/BF01213292]

21 **Cho DK**, Park SY, Kee WJ, Lee JH, Ki HS, Yoon KW, Cho SB, Lee WS, Joo YE, Kim HS, Choi SK, Rew JS. [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**: 368-375 [PMID: 20571304 DOI: 10.4166/kjg.2010.55.6.368]

22 **Graham DY**, Lew GM, Malaty HM, Evans DG, Evans DJ, Klein PD, Alpert LC, Genta RM. Factors influencing the eradication of Helicobacter pylori with triple therapy. *Gastroenterology* 1992; **102**: 493-496 [PMID: 1732120 DOI: 10.1016/0016-5085(92)90095-G]

23 **Horikawa C**, Kodama S, Fujihara K, Hirasawa R, Yachi Y, Suzuki A, Hanyu O, Shimano H, Sone H. High risk of failing eradication of Helicobacter pylori in patients with diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2014; **106**: 81-87 [PMID: 25110103 DOI: 10.1016/j.diabres.2014.07.009]

24 **Groop LC**, Luzi L, DeFronzo RA, Melander A. Hyperglycaemia and absorption of sulphonylurea drugs. *Lancet* 1989; **2**: 129-130 [PMID: 2567896 DOI: 10.1016/S0140-6736(89)90184-0]

25 **Kong MF**, Macdonald IA, Tattersall RB. Gastric emptying in diabetes. *Diabet Med* 1996; **13**: 112-119 [PMID: 8641114 DOI: 10.1002/(SICI)1096-9136(199602)13: 2<112: : AID-DIA37>3.0.CO; 2-H]

26 **Gwilt PR**, Nahhas RR, Tracewell WG. The effects of diabetes mellitus on pharmacokinetics and pharmacodynamics in humans. *Clin Pharmacokinet* 1991; **20**: 477-490 [PMID: 2044331 DOI: 10.2165/00003088-199120060-00004]

27 **Marhoffer W**, Stein M, Maeser E, Federlin K. Impairment of polymorphonuclear leukocyte function and metabolic control of diabetes. *Diabetes Care* 1992; **15**: 256-260 [PMID: 1547682 DOI: 10.2337/diacare.15.2.256]

28 **Mor A**, Berencsi K, Nielsen JS, Rungby J, Friborg S, Brandslund I, Christiansen JS, Vaag A, Beck-Nielsen H, Sørensen HT, Thomsen RW. Rates of Community-based Antibiotic Prescriptions and Hospital-treated Infections in Individuals With and Without Type 2 Diabetes: A Danish Nationwide Cohort Study, 2004-2012. *Clin Infect Dis* 2016; **63**: 501-511 [PMID: 27353662 DOI: 10.1093/cid/ciw345]

29 **Versalovic J**. Helicobacter pylori. Pathology and diagnostic strategies. *Am J Clin Pathol* 2003; **119**: 403-412 [PMID: 12645343 DOI: 10.1309/5DTF5HT7NPLNA6J5]

30 **Gatta L**, Vakil N, Ricci C, Osborn JF, Tampieri A, Perna F, Miglioli M, Vaira D. Effect of proton pump inhibitors and antacid therapy on 13C urea breath tests and stool test for Helicobacter pylori infection. *Am J Gastroenterol* 2004; **99**: 823-829 [PMID: 15128344 DOI: 10.1111/j.1572-0241.2004.30162.x]

31 **Mégraud F**, Lehours P. Helicobacter pylori detection and antimicrobial susceptibility testing. *Clin Microbiol Rev* 2007; **20**: 280-322 [PMID: 17428887 DOI: 10.1128/CMR.00033-06]

32 **Ferwana M**, Abdulmajeed I, Alhajiahmed A, Madani W, Firwana B, Hasan R, Altayar O, Limburg PJ, Murad MH, Knawy B. Accuracy of urea breath test in Helicobacter pylori infection: meta-analysis. *World J Gastroenterol* 2015; **21**: 1305-1314 [PMID: 25632206 DOI: 10.3748/wjg.v21.i4.1305]

33 **Leodolter A**, Wolle K, Malfertheiner P. Current standards in the diagnosis of Helicobacter pylori infection. *Dig Dis* 2001; **19**: 116-122 [PMID: 11549820 DOI: 10.1159/000050665]

**P-Reviewer:** Buzas GM, Karatapanis S, Slomiany BL, Suzuki H

**S-Editor:** Gong ZM **L-Editor:** **E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** South Korea

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C, C, C

Grade D (Fair): 0

Grade E (Poor): 0

G:\김성은-Active\김성은연구관련\2차제균HP\Helicobacter\슬라이드1.TIF

**Figure 1 Flowchart of the study participants.** ITT: intention-to-treat; PP: per-protocol; *H. pylori: Helicobacter pylori*.

G:\김성은-Active\김성은연구관련\2차제균HP\Helicobacter\슬라이드2.TIF

**Figure 2** ***Helicobacter pylori* eradication rates** **of second-line bismuth-based quadruple therapy according to years (*P* = 0.01).**

**Table 1 Baseline characteristics of the patients *n* (%)**

|  |  |
| --- | --- |
| **Variable** | **Patients (*n* = 6361)** |
| Age (yr, mean ± SD) | 54.6 ± 11.6 |
| Gender |  |
| Male | 354 (55.7) |
| Female | 282 (44.3) |
| Residence |  |
| Rural | 126 (19.8) |
| Urban | 510 (80.2) |
| Cigarette smoking | 174/605 (28.8) |
| Alcohol intake | 279/605 (46.1) |
| Diabetes mellitus | 61/605 (10.1) |
| Hypertension | 121/605 (20.0) |
| Endoscopic findings |  |
| Gastric ulcer | 205 (32.2) |
| Duodenal ulcer | 193 (30.3) |
| Gastric ulcer + Duodenal ulcer | 40 (6.3) |
| Post ESD due to adenoma or EGC | 91 (14.3) |
| Nodular gastritis | 29 (4.6) |
| Others2 | 78 (12.2) |

1Total number of enrolled patients; missing values are not included. The number behind the dash is the total number of subjects who answered each question. 2Others include MALT lymphoma, dyspepsia, gastric polyp and intestinal metaplasia. ESD: endoscopic submucosal dissection; EGC: early gastric cancer; MALT lymphoma: mucosa-associated lymphoid tissue lymphoma.

**Table 2** **Adverse effects after bismuth-based quadruple therapy *n* (%)**

|  |  |
| --- | --- |
|  | **Patients (*n* = 495)** |
| Side effect | 74 (14.9) |
| Diarrhea | 16 (3.2) |
| Bloating or abdominal pain | 22 (4.4) |
| Nausea or vomiting | 26 (5.3) |
| Others1 | 10 (2.0) |

1Others include myalgia, headache and bitter sensation in the mouth.

**Table 3** **Related factors about eradication failure of bismuth-based quadruple therapy *n* (%)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Eradication Success (*n* = 4681)** | **Eradication Failure (*n* = 271)** | ***P* valuea** | ***P* valuec** | **Adjusted**  **OR (95%CI)c** |
| Age (yr) |  |  |  |  |  |
| <50 | 124 (95.4) | 6 (4.6) |  |  |  |
| ≥ 50 | 344 (94.2) | 21 (5.8) | 0.822 | 0.752 | 1.17 (0.44-3.09) |
| Gender |  |  |  |  |  |
| Male | 248 (93.2) | 18 (6.8) |  |  |  |
| Female | 220 (96.1) | 9 (3.9) | 0.233 | 0.240 | 0.57 (0.22-1.46) |
| Residence |  |  |  |  |  |
| Rural | 90 (94.7) | 5 (5.3) |  |  |  |
| Urban | 378 (94.5) | 22 (5.5) | 1.000 | 0.783 | 1.16 (0.41-3.24) |
| Cigarette smoking |  |  |  |  |  |
| No | 341 (95.0) | 18 (5.0) |  |  |  |
| Yes | 111 (92.5) | 9 (7.5) | 0.359 | 0.435 | 1.48 (0.56-3.93) |
| Alcohol intake |  |  |  |  |  |
| No | 252 (94.4) | 15 (5.6) |  |  |  |
| Yes | 200 (94.3) | 12 (5.7) | 1.000 | 0.522 | 0.74 (0.29-1.89) |
| Diabetes mellitus |  |  |  |  |  |
| No | 408 (95.6) | 19 (4.4) |  |  |  |
| Yes | 44 (84.6) | 8 (15.4) | 0.005 | 0.004 | 3.99 (1.56-10.20) |
| Hypertension |  |  |  |  |  |
| No | 361 (94.5) | 21 (5.5) |  |  |  |
| Yes | 91 (93.8) | 6 (6.2) | 0.806 | 0.638 | 0.78 (0.28-2.18) |

1Total number of analyzed patients. Missing values are not included. a*p* < 0.05, univariate logistic regression test; c*p* < 0.05, multivariate logistic regression test. Logistic model including terms of age, gender, residence, cigarette smoking, alcohol intake, diabetes mellitus and hypertension.