

ORIGINAL ARTICLE

표준 삼제 요법에 실패한 헬리코박터 파일로리 감염 환자에서의 7일 Bismuth 포함 사제 요법과 14일 Moxifloxacin 포함 삼제 요법의 제균율 비교 연구

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Effect of 7-day Bismuth Quadruple Therapy versus 14-day Moxifloxacin Triple Therapy for Second-line *Helicobacter pylori* Eradication Therapy

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Background/Aims: Both bismuth-containing quadruple therapy and moxifloxacin-containing triple therapy have been suggested as second-line eradication therapy for *Helicobacter pylori* (*H. pylori*) infection. We aimed to evaluate the efficacy of 14-day moxifloxacin-containing triple therapy (14-EAM) in second-line *H. pylori* eradication in comparison to 7-day bismuth-containing quadruple therapy (7-RBMT).

Methods: From January 2011 to December 2015, a total of 569 patients who failed to respond to first-line triple therapy and who subsequently received second-line 7-RBMT or 14-EAM were retrospectively enrolled. The eradication rates were identified using per-protocol (PP) analysis. *H. pylori* eradication was confirmed by a ¹³C-urea breath test (UBiT-IR300[®]; Otsuka Electronics, Co., Ltd., Osaka, Japan) or a rapid urease test (CLOtest[®]; Delta West, Bentley, Australia) at least 4 weeks after completion of eradication therapy.

Results: A total of 487 and 82 patients received 7-RBMT and 14-EAM, respectively. PP eradication rates were 93.6% (366/391; 95% CI, 91.0-95.9%) with 7-RBMT and 73.8% (48/65; 95% CI, 63.1-84.6%) with 14-EAM ($p < 0.001$). Therefore, the eradication rates with 7-RBMT were significantly higher than with 14-EAM according to the PP analysis. The adverse event rate was 17.1% (67/391) with 7-RBMT and 7.7% (5/65) with 14-EAM ($p = 0.065$). In terms of risk factors, multivariate analysis revealed that 14-EAM (OR, 5.47; 95% CI, 2.74-10.93) was related to *H. pylori* eradication failure.

Conclusions: 7-RBMT may be an effective second-line therapy in patients who failed to respond to first-line triple therapy in Korea, where there is a high prevalence of *H. pylori* infection. (Korean J Gastroenterol 2019;73:26-34)

Key Words: *Helicobacter pylori*; Disease eradication; Bismuth tripotassium dicitrate; Moxifloxacin

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most common causes of chronic bacterial infection in humans: it is thought that nearly one-half of the entire world population has been infected by *H. pylori*.¹ In addition, *H. pylori* is widely known to be related to chronic gastritis, peptic ulcers, mucosa-associated lymphoid tissue lymphoma, and gastric cancer. Therefore, the International Agency for Research on Cancer, a branch of the World Health Organization, categorizes *H. pylori* as a definite gastric carcinogen (group I).²

The eradication of *H. pylori* is a serious issue for improving public health. However, the efficacy of first-line clarithromycin-containing triple therapy, which is generally composed of proton pump inhibitor (PPI), amoxicillin, and clarithromycin, is consistently declining worldwide.³ This tendency is similar in Korea, and the eradication rates of *H. pylori* using clarithromycin-containing triple therapy, reported at 84.9-87.5% from 2001 to 2007 and 80.0-81.4% from 2008 to 2010 ($p < 0.0001$), have shown a decreasing trend over the past 10 years in Korea.⁴ Thus, a potent second-line regimen is required for successful *H. pylori* eradication.

There are several guidelines for *H. pylori* eradication in the East and the West, and various regimens are recommended for second-line therapy. Bismuth-containing quadruple therapy, usually consisting of bismuth, tetracycline, metronidazole, and PPI, is recommended in Korea⁵ and China.⁶ However, metronidazole-containing triple therapy, which is composed of amoxicillin, metronidazole, and PPI, is recommended in Japan.⁷ According to Western guidelines, the Maastricht V/Florence consensus report recommended a bismuth-containing quadruple therapy or a fluoroquinolone-containing triple therapy for second-line therapy for *H. pylori* eradication in patients who failed clarithromycin-containing triple therapy.⁸ Several studies evaluated the *H. pylori* eradication rates between bismuth-containing quadruple therapy and fluoroquinolone-containing triple therapy; however, the results are conflicting.⁹⁻¹² From this background, the aims of this study are to investigate the efficacy, compliance, and adverse effects of 14-day moxifloxacin-containing triple therapy in second-line *H. pylori* eradication compared with 7-day bismuth-containing quadruple therapy.

SUBJECTS AND METHODS

1. Study population

Patients who failed first-line 7-day clarithromycin-containing triple therapy (standard-dose PPI, 1.0 g amoxicillin, and 0.5 g clarithromycin, twice daily) and who received second-line *H. pylori* eradication therapy at either Kosin University Gospel Hospital or Dong-eui Medical Center, which are located in the same city in Korea, from January 2011 to December 2015 were retrospectively enrolled in the current study. *H. pylori* positivity was confirmed using a ¹³C-urea breath test (UBiT-IR300®; Otsuka Electronics, Co., Ltd., Osaka, Japan) or a rapid urease test (CLOtest®; Delta West, Bentley, Australia) before and after eradication therapy. Patients with poor compliance or who were lost to follow-up were excluded. Patients lost to follow-up were defined as patients who received the second-line *H. pylori* eradication therapy with unknown results, regardless of eradication success or failure. Compliance was classified as good or poor according to the pill count in the medical records. Patients who took 80% or more of their prescribed medicine were placed in the good compliance category, and those who took <80% of their prescribed medicine were included in the poor compliance category.

Demographic features, such as smoking and alcohol habits, diabetes mellitus, hypertension, endoscopic diagnoses, and adverse events associated with eradication therapy, were also evaluated. All patients underwent endoscopy, and endoscopic diagnoses (e.g., gastric ulcers, duodenal ulcers, gastric and duodenal ulcers, a previous endoscopic submucosal dissection state due to adenoma or early gastric cancer, mucosa-associated lymphoid tissue lymphoma, nodular gastritis, gastric polyps, or dyspepsia) were verified by endoscopy or endoscopy with a biopsy. The occurrence of adverse events after eradication therapy was confirmed by a review of the patient's medical records. The Institutional Review Board of Kosin University Gospel Hospital approved this study (IRB file No. 2016-10-021).

2. *H. pylori* eradication therapy and follow-up

We prescribed 7-day bismuth-containing quadruple therapy for patients at Kosin University Gospel Hospital and 14-day moxifloxacin-containing triple therapy for patients at Dong-eui Medical Center for second-line *H. pylori* eradication therapy. Bismuth-containing quadruple therapy consisted of 20 mg of

rabeprazole twice daily, 300 mg of tripotassium dicitrato bismuthate, 500 mg of metronidazole three times daily, and 500 mg of tetracycline four times daily for 7 days (7-RBMT). Moxifloxacin-containing triple therapy was comprised of 40 mg of esomeprazole twice daily, 1.0 g of amoxicillin twice daily, and 400 mg of moxifloxacin once daily for 14 days (14-EAM). A ^{13}C -urea breath test (UBiT-IR300[®]) or a rapid urease test (CLOtest[®]) was conducted to assess *H. pylori* eradication at least 4 weeks after treatment completion. Before the ^{13}C -urea breath test (UBiT-IR300[®]) or rapid urease test (CLOtest[®]), patients suspended PPI or histamine (H_2) receptor antagonist treatment for at least 2 weeks.

3. Rapid urease test (CLOtest[®])

An endoscopic biopsy of the gastric mucosa was performed to verify *H. pylori* infection with the rapid urease test (CLOtest[®]). The site of the gastric mucosal biopsy was the antrum and/or corpus, and normal or near-normal gastric mucosa with little atrophy or intestinal metaplasia was obtained. The tissue sample was immersed in rapid urea reagent. The result was considered positive when the reagent color changed from yellow to red within 12 hours. If there was no change in the reagent color, it was considered negative.

4. ^{13}C -urea breath test (UBiT-IR300[®])

Prior to collection of the first breath sample, patients fasted for at least 4 hours. Afterwards, patients took 100 mg tablets of ^{13}C -urea (UBiTKit[™], Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) with 100 mL of water orally, and the second breath sample was collected 20 minutes after taking the tablets. The obtained breath samples were analyzed using the ^{13}C -urea breath test (UBiT-IR300[®]). The cut-off value in the procedure was set at 2.5‰.

5. Statistical analyses

All statistical analyses were performed with the Statistical Package for the Social Sciences software version 20.0 (SPSS Inc., Chicago, IL, USA). The *H. pylori* eradication rate was identified by per-protocol (PP) analysis. Patients with poor compliance or those lost to follow-up were excluded when we conducted the PP analysis. The trends in eradication rates of *H. pylori* were analyzed with linear-by-linear association. Categorical variables were analyzed using Chi-square (χ^2) tests, and continuous variables were analyzed using Student's t-tests. Univariate and multivariate logistic regression tests were utilized for identification of risk factors and presented as an OR and 95% CI. A p-value of <0.05 was considered statistically significant.

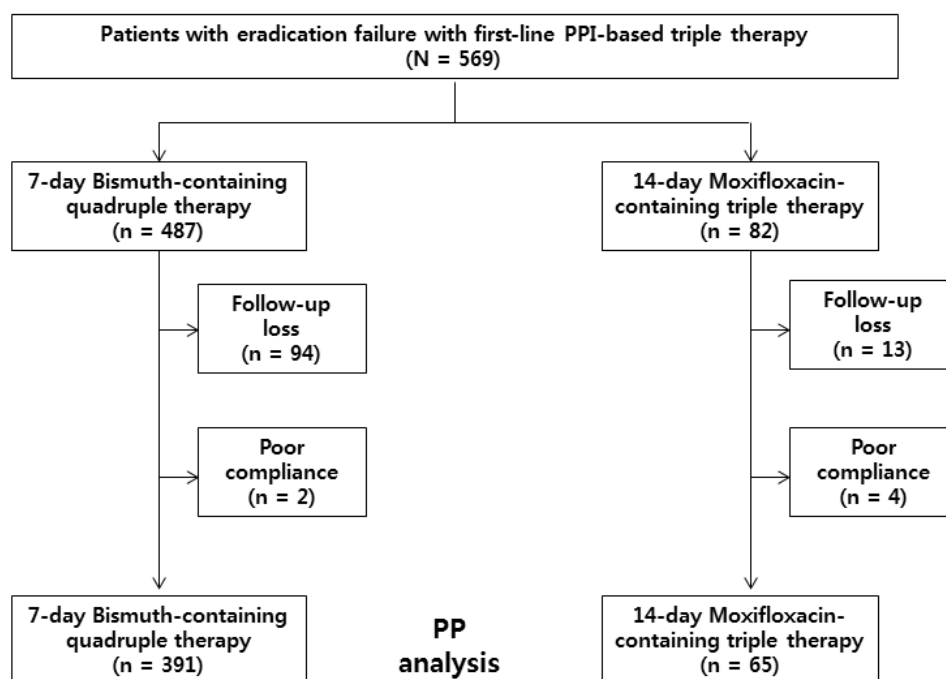


Fig. 1. Flowchart of study participants. PPI, proton pump inhibitor; PP, per-protocol.

RESULTS

1. Patient characteristics

Between January 2011 to December 2015, 569 patients failed the first-line clarithromycin-containing triple therapy. Initially, 487 patients received 7-RBMT and 82 patients received 14-EAM for second-line eradication therapy. In the 7-RBMT group, 94 patients (19.3%) were lost to follow-up and two patients (0.4%) were excluded due to poor compliance. In the 14-EAM group, 13 patients (15.9%) were lost to follow-up and four patients (4.9%) were excluded due to poor compliance. Therefore, 391 patients in the 7-RBMT group and 65 patients in the 14-EAM group were included as subjects for PP analysis (Fig. 1).

Among the baseline characteristics, the proportion of patients with a history of cigarette smoking (60.5% vs. 44.7%, respectively; $p=0.011$), and alcohol intake (38.3% vs. 26.6%, respectively; $p=0.034$) was statistically higher in the 14-EAM group. In terms of the endoscopic diagnosis, the rate of gastric ulcer occurrence was statistically higher in the 14-EAM group (47.6% vs. 34.4%, respectively; $p=0.025$); however, the rate of post endoscopic submucosal dissection was statistically higher in the 7-RBMT group (13.2% vs. 2.4%, respectively; $p=0.003$). There were no significant differences in age, diabetes, hypertension, or other endoscopic findings between the two groups (Table 1).

Table 1. Baseline Characteristics of the Subjects

Variable	7-day bismuth-containing quadruple therapy (n=487 ^b)	14-day moxifloxacin-containing triple therapy (n=82 ^b)	p-value
Age (years)	54.3±11.5	55.7±11.9	0.311
Gender			0.072
Male	261 (53.6)	53 (64.6)	
Female	226 (46.4)	29 (35.4)	
Cigarette smoking	215/481 (44.7)	49/81 (60.5)	0.011 ^a
Alcohol intake	128/481 (26.6)	31/81 (38.3)	0.034 ^a
Diabetes mellitus	53/481 (11.0)	6/81 (7.4)	0.433
Hypertension	95/481 (19.8)	21/81 (25.9)	0.235
Endoscopic diagnosis			
Gastric ulcer	167 (34.4)	39 (47.6)	0.025 ^a
Duodenal ulcer	141 (29.0)	22 (26.8)	0.792
Gastric ulcer+duodenal ulcer	26 (5.3)	2 (2.4)	0.407
Post ESD due to adenoma or EGC	66 (13.2)	2 (2.4)	0.003 ^a
Others ^c	87 (18.1)	17 (20.8)	0.538

Values are presented as mean±standard deviation or n (%).

ESD, endoscopic submucosal dissection; EGC, early gastric cancer; MALT, mucosa-associated lymphoid tissue.

^aIndicates statistical significance; ^bTotal number of enrolled patients. Missing values were not included. The number behind the dash is the total number of subjects who answered each question; ^cOthers include MALT lymphoma, dyspepsia, gastric polyp and gastritis.

Table 2. Outcomes of the Eradication Therapies

	7-day bismuth-containing quadruple therapy (n=487)	14-day moxifloxacin-containing triple therapy (n=82)	p-value
Eradication rate			
Per-protocol	366/391 (93.6)	48/65 (73.8)	<0.001 ^a
95% CI	91.0-95.9	63.1-84.6	
Compliance	485 (99.6)	78 (95.1)	0.005 ^a

Values are presented as n (%).

CI, confidence interval.

^aIndicates statistical significance.

2. *H. pylori* eradication rates

Table 2 reveals the eradication rate of *H. pylori* based on the PP analysis, and Fig. 2 presents the annual eradication rates of *H. pylori* according to each eradication regimen. The eradication rates by PP analysis were 93.6% (366/391; 95% CI, 91.0-95.9%) and 73.8% (48/65; 95% CI, 63.1-84.6%) in the 7-RBMT group and 14-EAM group, respectively ($p<0.001$).

Annual eradication rates from 2011 to 2015 were 92.2%, 95.5%, 92.4%, 94.1%, and 92.5%. Consecutively, in the 7-RBMT group ($p=0.579$) and 75.0%, 71.4%, 75.0%, 73.7%, and 75.0%, consecutively, in the 14-EAM group by PP analysis ($p=0.932$) (Fig. 2). The compliance rate was significantly higher in the 7-RBMT group (99.6% vs. 95.1%, respectively;

3. Adverse effects of eradication therapy

Adverse effects were recorded in 67 patients (17.1%) in the 7-RBMT group and five patients (7.7%) in the 14-EAM group ($p=0.065$). The adverse events were mild or moderate in all patients. The most common adverse events were nausea or vomiting (23/391, 5.9%), bloating or abdominal pain (19/391, 4.9%), and diarrhea (15/391, 3.9%) in the 7-RBMT group, and diarrhea (2/65, 3.1%), bloating or abdominal pain (1/65, 1.5%), nausea or vomiting (1/65, 1.5%), and skin rash (1/65, 1.5%) in the 14-EAM group (Table 3).

4. Related factors for eradication failure

Table 4 shows the related factors for eradication failure.

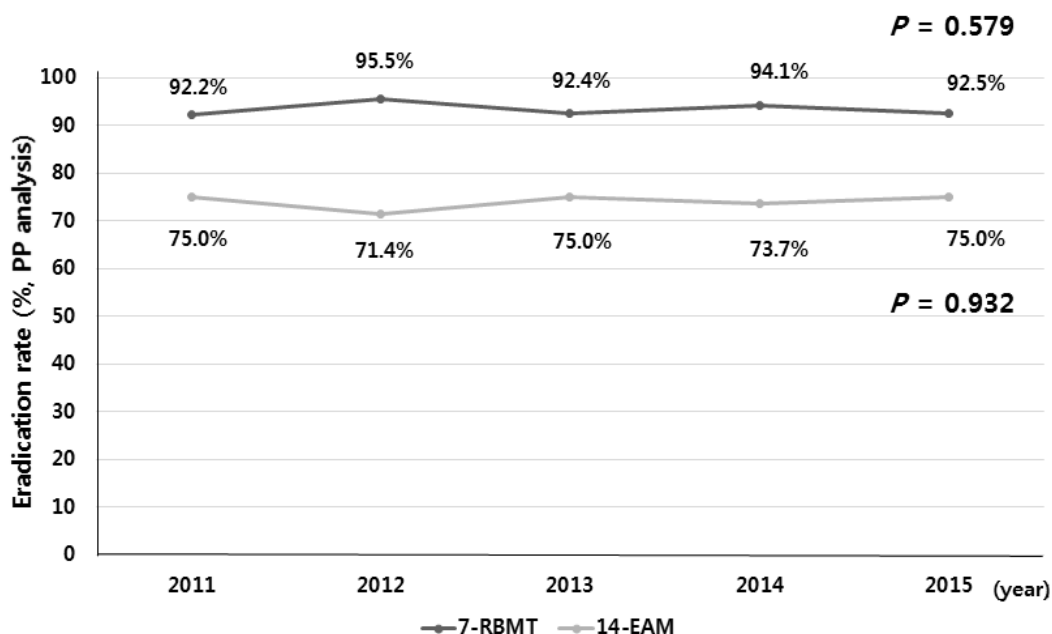


Fig. 2. *Helicobacter pylori* eradication rates of second line 7-day bismuth-containing quadruple therapy (●, $p=0.579$) and 14-day moxifloxacin-containing triple therapy (●, $p=0.932$) according to year. PP, per-protocol.

Univariate analysis verified that female ($p=0.036$) and

Table 3. Side Effects after the Eradication Therapies

	7-day bismuth-containing quadruple therapy (n=391)	14-day moxifloxacin-containing triple therapy (n=65)	p-value
Diarrhea	15 (3.9)	2 (3.1)	1.000
Bloating or abdominal pain	19 (4.9)	1 (1.5)	0.334
Nausea or vomiting	23 (5.9)	1 (1.5)	0.228
Skin rash	2 (0.5)	1 (1.5)	0.370
Others ^a	8 (2.1)	0 (0)	-
Total	67 (17.1)	5 (7.7)	0.065

Values are presented as n (%).

^aOthers include myalgia, headache and bitter sensation in the mouth.

14-EAM ($p<0.001$) were significantly associated with eradication failure. 14-EAM (OR, 5.47; 95% CI, 2.74-10.93; $p<0.001$) was significantly related to *H. pylori* eradication therapy failure. There was no statistically significant association between eradication failure and other factors, such as age, gender, residence, smoking, alcohol, diabetes mellitus, and hypertension.

DISCUSSION

Bismuth-containing quadruple therapy is a widely used second-line *H. pylori* eradication therapy, but moxifloxacin-containing triple therapy has been suggested as an alternative second-line therapy for *H. pylori* infection.^{8,12,13} A meta-analysis study reported that moxifloxacin-containing triple therapy was more effective than bismuth-containing quadruple therapy in the second-line eradication of *H. pylori*.¹² However, a recent

study in Korea revealed that 7-RBMT has remained efficacious as a second-line regimen over the last 10 years, and there have been no significant changes in eradication rates with time (eradication rate range: 83.2-93.7%, $p=0.352$).⁴ In addition, the eradication rates of 14-day moxifloxacin-containing triple therapy range from 82.8-98.1%, which are similar to those of bismuth-containing quadruple therapy.¹⁴ Several studies have investigated the effects of second-line *H. pylori* eradication therapies, including bismuth-containing quadruple therapy and moxifloxacin-containing triple therapy.¹² However, to the best of our knowledge, this is the first study to directly compare 7-day bismuth-containing quadruple therapy and 14-day moxifloxacin-containing triple therapy.

Generally, well-known correlating factors of *H. pylori* eradication failure include resistance to antibiotic agents and poor patient compliance with regard to medication.¹⁵ In the case of first-line triple therapy, clarithromycin resistance is a critical

Table 4. Clinical Factors Related to Eradication Failure of Second-line Eradication Therapies

	Eradication success (n=414)	Eradication failure (n=42)	Univariate p-value	Multivariate p-value ^b	Adjusted OR (95% CI) ^b
Age (years)	54.4±11.5	53.2±12.6	0.505	0.447	0.99 (0.96-1.02)
Gender					
Male	228 (93.4)	16 (6.6)			
Female	186 (87.7)	26 (12.3)	0.036 ^a	0.119	1.73 (0.87-3.44)
Eradication therapy					
7-RBMT	366 (93.6)	25 (6.4)			
14-EAM	48 (73.8)	17 (26.2)	<0.001 ^a	<0.001 ^a	5.47 (2.74-10.93) ^a
Residence					
Rural	90 (90.9)	9 (9.1)			
Urban	324 (90.8)	33 (9.2)	0.963	0.411	0.71 (0.31-1.61)
Cigarette smoking					
No	296 (90.8)	30 (9.2)			
Yes	114 (91.2)	11 (8.8)	0.894	0.301	1.61 (0.65-3.98)
Alcohol intake					
No	217 (88.9)	27 (11.1)			
Yes	193 (93.2)	14 (6.8)	0.113	0.522	0.75 (0.32-1.79)
Diabetes mellitus					
No	363 (90.8)	37 (9.2)			
Yes	47 (92.2)	4 (7.8)	1.000	0.92	0.94 (0.30-2.96)
Hypertension					
No	324 (91.0)	32 (9.0)			
Yes	86 (90.5)	9 (9.5)	0.843	0.520	1.32 (0.57-3.09)

Values are presented as mean±standard deviation or n (%).

OR, odds ratio; CI, confidence interval; 7-RBMT, 7-day bismuth-containing quadruple therapy; 14-EAM, 14-day moxifloxacin-containing triple therapy.

^aIndicates statistical significance; ^bLogistic model including terms of age, gender, type of eradication therapy, residence, cigarette smoking, alcohol intake, diabetes mellitus and hypertension.

determinant for eradication success. For bismuth-containing quadruple therapy, metronidazole resistance is considered an important factor for deciding the success of eradication,¹⁶ because resistance to tetracycline is low in the most countries.^{17,18} Even in Korea where the antibiotic resistance rate of *H. pylori* is high, the resistance rate to tetracycline was reported to be similar for the past 11 years ($p=0.761$),¹⁹ whereas the rate of metronidazole resistance is usually 20-40% in Western countries and 50-80% in developing countries.²⁰ A recent study in Korea demonstrated that the resistance rate of metronidazole was stable from 2003-2012 ($p=0.418$) with a prevalence of 26.0-35.8%.²¹ Resistance to fluoroquinolones also affects the *H. pylori* eradication rate, and, unfortunately, the prevalence of fluoroquinolone resistance is rapidly increasing worldwide.¹⁶ A recent study reported a high rate of resistance to levofloxacin (53.01%), moxifloxacin (46.57%), and ciprofloxacin (44.28%) in Italy.²² Lee et al.²¹ also revealed the prevalence of levofloxacin (34.6%) and moxifloxacin (34.6%) resistance in Korea, and showed that the resistance rates of levofloxacin ($p<0.001$) and moxifloxacin ($p<0.001$) significantly increased over the past 10 years. When they analyzed the data by the primary and secondary resistance, a statistically significant increase was shown in the secondary resistance rate to moxifloxacin ($p=0.025$); the prevalence of secondary moxifloxacin resistance was 50.0% from 2009 to 2012.

In the current study, the *H. pylori* eradication failure rate associated with 14-EAM was significantly higher than that associated with 7-RBMT; the OR was 5.47 ($p<0.001$). The *H. pylori* eradication rate for second-line 7-RBMT was identified as 93.6% in PP analysis. However, the eradication rate of moxifloxacin-containing triple therapy was unsuitable for the generally accepted standard. In general, acceptable *H. pylori* eradication therapies should have a success rate of at least 90% irrespective of the presence of antibiotic resistance.^{16,23} Unfortunately, we were unable to evaluate the antibiotic resistant state of *H. pylori* due to the retrospective design of this study. Nevertheless, when we reflect upon previous studies concerning the antibiotic susceptibility of *H. pylori* in Korea, bismuth-containing quadruple therapy might be considered for second-line *H. pylori* eradication therapy in Korea.

With regard to the treatment duration, the shorter treatment duration seen with bismuth-containing quadruple therapy was more effective than the longer treatment duration associated

with moxifloxacin-containing triple therapy in this study. Treatment duration of bismuth-containing quadruple therapy is an important factor in eradication success when the traditional bismuth-containing quadruple therapy is prescribed.²⁴ It is known that metronidazole resistance could be overcome by prolongation of treatment duration.²⁵ A meta-analysis study revealed that bismuth-containing quadruple therapy for 10-14 days was more efficient than when it was given for either 1-3 days, 4 days, or 7 days.²⁶ However, this is thought to be applicable only to first-line *H. pylori* quadruple eradication therapies. In patients who are non-naïve to *H. pylori* eradication therapy, namely, those who failed first-line eradication therapy, the 7-day treatment duration of bismuth-containing quadruple therapy seemed sufficient.²³ Several studies reported that the eradication rates of second-line bismuth-containing quadruple therapy were similar in patients with treatment durations of 7, 10, and 14 days.^{27,28} A recent randomized controlled trial in Korea also reported that the 7-day second-line bismuth-containing quadruple therapy was not statistically inferior to the 14-day bismuth-containing quadruple therapy.²⁹ Even if 7-day bismuth-containing quadruple therapy showed unacceptable eradication rates in areas where antibiotic resistance to metronidazole is $\geq 40\%$,²⁴ more studies are required to investigate the efficacy, cost, safety, and ideal duration of bismuth-containing quadruple therapy as a second-line eradication therapy.

Although there was no statistical difference, the rate of adverse effects in the 7-RBMT group tended to be higher than that of the 14-EAM group in this study. A meta-analysis reported that the rate of side effects associated with moxifloxacin-containing triple therapy was statistically lower than that of bismuth-containing quadruple therapy (OR, 0.27; 95% CI, 0.18-0.4).¹² Recently, a single capsule with a composite of bismuth, metronidazole, and tetracycline has been developed to make the bismuth-containing quadruple therapy simpler for patients, and the results of studies of this new medication, including eradication rate, compliance, and safety profiles, were inspiring.^{30,31} Therefore, the compliance and adverse effect rates of bismuth-containing quadruple therapy is expected to improve in the future.

This study has several limitations. First, many patients in the present study were lost to follow-up. In addition, there was a large difference in the number of patients between the two group. These could affect the results as bias. Second, we did not investigate cytochrome P450 2C19 (CYP2C19) me-

tabolism, which induces many drug metabolism pathways, including that for PPI. Therefore, a disparity in CYP2C19 genotypes can influence the eradication rate. In addition, the rates of cigarette smoking and alcohol intake were higher in the 14-EAM group compared to the 7-RBMT group. In previous studies, several factors have been presumed to be the cause of eradication failure, including age, sex, smoking, alcohol, and diabetes.³²⁻³⁵ However, a direct relationship between these factors and eradication failure remains controversial.³²⁻³⁵ Therefore, it is uncertain but unlikely that these factors could have had a significant influence on the current study.

In conclusion, compared to 14-day moxifloxacin-containing triple therapy, 7-day bismuth-containing quadruple therapy might provide benefits for patients who failed first-line triple therapy. In addition, the present study suggests that the poor compliance and high adverse event rates associated with bismuth-containing quadruple therapy could be overcome by its relative short duration for eradication therapy. Additional well-designed, prospective, large-scale studies are required to confirm the appropriate second-line therapy for *H. pylori* eradication.

REFERENCES

1. Pounder RE, Ng D. The prevalence of *Helicobacter pylori* infection in different countries. *Aliment Pharmacol Ther* 1995;9 Suppl 2: S33-S39.
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.
3. Yeo YH, Shiu SI, Ho HJ, et al. First-line *Helicobacter pylori* eradication therapies in countries with high and low clarithromycin resistance: a systematic review and network meta-analysis. *Gut* 2018;67:20-27.
4. Shin WG, Lee SW, Baik GH, et al. 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.
5. Kim SG, Jung HK, Lee HL, et al. Guidelines for the diagnosis and treatment of *Helicobacter pylori* infection in Korea, 2013 revised edition. *J Gastroenterol Hepatol* 2014;29:1371-1386.
6. Chinese Society of Gastroenterology, Chinese Study Group on *Helicobacter pylori*, Liu WZ, Xie Y, et al. Fourth Chinese national consensus report on the management of *Helicobacter pylori* infection. *J Dig Dis* 2013;14:211-221.
7. Asaka M. A new approach for elimination of gastric cancer deaths in Japan. *Int J Cancer* 2013;132:1272-1276.
8. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection-the Maastricht V/Florence consensus report. *Gut* 2017;66:6-30.
9. Lee ST, Lee DH, Lim JH, et al. 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.
10. Cao Z, Chen Q, Zhang W, et al. Fourteen-day optimized levofloxacin-based therapy versus classical quadruple therapy for *Helicobacter pylori* treatment failures: a randomized clinical trial. *Scand J Gastroenterol* 2015;50:1185-1190.
11. Kim MS, Kim N, Kim SE, et al. Long-term follow up *Helicobacter pylori* reinfection rate after second-line treatment: bismuth-containing quadruple therapy versus moxifloxacin-based triple therapy. *BMC Gastroenterol* 2013;13:138.
12. Wu C, Chen X, Liu J, Li MY, Zhang ZQ, Wang ZQ. Moxifloxacin-containing triple therapy versus bismuth-containing quadruple therapy for second-line treatment of *Helicobacter pylori* infection: a meta-analysis. *Helicobacter* 2011;16:131-138.
13. Zagari RM, Romano M, Ojetti V, et al. Guidelines for the management of *Helicobacter pylori* infection in Italy: the III working group consensus report 2015. *Dig Liver Dis* 2015;47:903-912.
14. Hwang JJ, Lee DH, Lee AR, et al. Efficacy of 14-d vs 7-d moxifloxacin-based triple regimens for second-line *Helicobacter pylori* eradication. *World J Gastroenterol* 2015;21:5568-5574.
15. Mégraud F. *H. pylori* antibiotic resistance: prevalence, importance, and advances in testing. *Gut* 2004;53:1374-1384.
16. Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. *Gut* 2010;59:1143-1153.
17. Megraud F, Coenen S, Versporten A, et al. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013;62:34-42.
18. Boyanova L, Mitov I. Geographic map and evolution of primary *Helicobacter pylori* resistance to antibacterial agents. *Expert Rev Anti Infect Ther* 2010;8:59-70.
19. Lee JY, Kim N, Kim MS, et al. Factors affecting first-line triple therapy of *Helicobacter pylori* including CYP2C19 genotype and antibiotic resistance. *Dig Dis Sci* 2014;59:1235-1243.
20. Mégraud F, Lehours P. *Helicobacter pylori* detection and antimicrobial susceptibility testing. *Clin Microbiol Rev* 2007;20: 280-322.
21. Lee JW, Kim N, Kim JM, et al. Prevalence of primary and secondary antimicrobial resistance of *Helicobacter pylori* in Korea from 2003 through 2012. *Helicobacter* 2013;18:206-214.
22. Di Giulio M, Di Campli E, Di Bartolomeo S, et al. In vitro antimicrobial susceptibility of *Helicobacter pylori* to nine antibiotics currently used in Central Italy. *Scand J Gastroenterol* 2016;51: 263-269.
23. Gisbert JP, McNicholl AG. Optimization strategies aimed to increase the efficacy of *H. pylori* eradication therapies. *Helicobacter* 2017;22:e.12392.
24. Lu H, Zhang W, Graham DY. Bismuth-containing quadruple therapy for *Helicobacter pylori*: lessons from China. *Eur J Gastroenterol Hepatol* 2013;25:1134-1140.
25. Mégraud F, Lamouliatte H. Review article: the treatment of refractory *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2003;17:1333-1343.

26. Fischbach L, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for *Helicobacter pylori*. *Aliment Pharmacol Ther* 2007; 26:343-357.
27. Gisbert JP, Pajares JM. Review article: *Helicobacter pylori* "rescue" regimen when proton pump inhibitor-based triple therapies fail. *Aliment Pharmacol Ther* 2002;16:1047-1057.
28. de Boer WA, Driessen WM, Potters VP, Tytgat GN. Randomized study comparing 1 with 2 weeks of quadruple therapy for eradicating *Helicobacter pylori*. *Am J Gastroenterol* 1994;89:1993-1997.
29. Chung JW, Lee JH, Jung HY, et al. Second-line *Helicobacter pylori* eradication: a randomized comparison of 1-week or 2-week bismuth-containing quadruple therapy. *Helicobacter* 2011;16: 289-294.
30. Malfertheiner P, Bazzoli F, Delchier JC, 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: 905-913.
31. 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.
32. Kim SE, Park MI, Park SJ, et al. Second-line bismuth-containing quadruple therapy for *Helicobacter pylori* eradication and impact of diabetes. *World J Gastroenterol* 2017;23:1059-1066.
33. Suzuki T, Matsuo K, Ito H, et al. Smoking increases the treatment failure for *Helicobacter pylori* eradication. *Am J Med* 2006;119: 217-224.
34. 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.
35. Kim SE, Park MI, Park SJ, et al. 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.