


A randomized controlled trial to compare *Helicobacter pylori* eradication rates between the empirical concomitant therapy and tailored therapy based on 23S rRNA point mutations

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Abstract

Background: Increasing clarithromycin resistance has led to changes in several guidelines for treatment of *Helicobacter pylori* infections. We compared the *H. pylori* eradication rates of the empirical concomitant therapy (CoT) and a tailored therapy (TaT) using dual-priming oligonucleotide-based polymerase chain reaction to detect mutations in the 23S rRNA gene that are related to clarithromycin resistance.

Methods: Between June 2020 and May 2021, 290 patients were enrolled and randomly assigned to 2 groups. In the CoT group, the patients received rabeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg, and metronidazole 500 mg twice daily for 14 days. In the TaT group, point mutation-negative patients received rabeprazole 20 mg, amoxicillin 1 g, and clarithromycin 500 mg twice daily for 14 days and point mutation-positive patients received rabeprazole 20 mg twice daily, metronidazole 500 mg thrice daily, and bismuth 120 mg and tetracycline 500 mg 4 times daily for 14 days.

Results: A total of 290 and 261 patients were included in the intention-to-treat (ITT) and per-protocol (PP) analyses, respectively. A2142G and/or A2143G point mutations were identified in 28.6% of the patients. No significant difference in eradication rates were observed between the 2 groups as per ITT (CoT, 82.8% and TaT, 85.5%, $P = .520$) and PP (CoT, 88.6% and TaT, 94.6%, $P = .084$) analyses. In point mutation-positive patients, the eradication rates in the CoT group were lower than those in the TaT group as per ITT (69.8% and 87.5%, respectively, $P = .050$) and PP (76.9% and 97.1%, respectively, $P = .011$) analyses.

Conclusion: CoT and TaT showed similar overall eradication rates for *H. pylori*. However, CoT eradication rate was suboptimal, especially in point mutation-positive patients.

Abbreviations: BQT = bismuth quadruple therapy, CoT = concomitant therapy, DPO-PCR = dual-priming oligonucleotide-based polymerase chain reaction, *H. pylori* = *Helicobacter pylori*, ITT = intention-to-treat, P-CAB = potassium competitive acid blocker, PAM = PPI, amoxicillin metronidazole, PP = per-protocol, PPI = proton-pump inhibitor, rRNA = ribosomal RNA, TaT = tailored therapy.

Keywords: clarithromycin resistance, concomitant therapy, eradication rate, *Helicobacter pylori*, polymerase chain reaction, tailored therapy

1. Introduction

Multiantibiotic regimens containing antisecretory agents are used to eradicate *Helicobacter pylori* infections.^[1–6] Triple therapy, which involves a proton-pump inhibitor (PPI), amoxicillin,

and clarithromycin, was used as the first-line treatment for *H. pylori* infections in Korea and Japan.^[7,8] However, growing resistance to antibiotics, such as clarithromycin, metronidazole, and levofloxacin, has decreased the eradication rates.^[9,10] In particular, the eradication rate of the triple therapy declined

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significantly for strains exhibiting clarithromycin resistance.^[11] Moreover, increasing the duration of clarithromycin treatment cannot improve the eradication rate of triple therapy in case of clarithromycin-resistant strains.^[12,13] Therefore, several European and American guidelines recommend discontinuing the use of triple therapy without antibiotic susceptibility testing in regions where clarithromycin resistance is >15%.^[1-3] Concomitant therapy (CoT) is the preferred regimen among nonbismuth quadruple regimens because it shows higher eradication rates than sequential therapy in case of clarithromycin or metronidazole resistance.^[14,15]

The culture-based antimicrobial susceptibility test is an ideal method for selecting a regimen to successfully eradicate *H. pylori*. However, it is time consuming, expensive, and often difficult to perform.^[16] Dual-priming oligonucleotide-based polymerase chain reaction (DPO-PCR) and sequencing tests can rapidly and conveniently detect the A2142G and/or A2143G point mutations in 23S ribosomal RNA (rRNA) that are related to clarithromycin resistance.^[17] Tailored therapy (TaT) based on DPO-PCR for point mutations related to clarithromycin resistance is helpful for clinicians in deciding the first-line treatment regimen for patients in areas with high clarithromycin resistance. A revised Korean guideline recommends a 7-day standard triple therapy as the first-line treatment if mutations in the 23S rRNA gene related to clarithromycin resistance are detected through PCR or sequencing.^[6] In patients infected with *H. pylori* strains harboring A2142G and/or A2143G point mutations, PPI, amoxicillin, metronidazole (PAM), or bismuth quadruple therapy (BQT) are recommended.^[5,6]

However, a recent prospective multicenter study failed to show the superiority of eradication rate of TaT (14-day triple therapy in patients without point mutation and 14-day PAM therapy in patients with point mutation) compared with that of CoT, based on detection of 23S rRNA gene point mutations, and the eradication rate of 14-day PAM therapy was 70.5% in the per-protocol (PP) analysis.^[18] In addition, in a previous retrospective study on patients with point mutations, a higher eradication rate was reported for TaT, composed of a BQT, compared with that for PAM.^[19] Therefore, we aimed to compare the eradication rates of the empirical CoT and TaT using BQT instead of PAM in patients with point mutations in the 23S rRNA gene.

2. Materials and Methods

2.1. Participants and inclusion criteria

This was a prospective, randomized controlled, multicenter study to compare the eradication rates of CoT and DPO-PCR-guided TaT comprising BQT and triple therapy. Patients who underwent endoscopy and were diagnosed with *H. pylori* infection were recruited at 6 tertiary care hospitals (Busan Paik Hospital, Kosin University College of Medicine, Pusan National University Hospital, Haeundae Paik Hospital, Dong-A University Hospital, and Pusan National University Yangsan Hospital) in Busan and Gyeongnam-do, South Korea, from June 2020 to May 2021. Eligible patients were randomly assigned to either CoT or TaT groups using a randomization table stratified by age, sex, and eradication indication by the computer. Allocation ratio was 1:1 between the groups. After assignment, participants and physicians were no longer blinded to the eradication regimens.

Participants who were (i) younger than 18 years of age, (ii) had undergone *H. pylori* eradication treatment, (iii) had a history of gastric surgery, (iv) had severe comorbidity, (v) had a history of antibiotic allergy, (vi) had a history of antibiotic use within 4 weeks of study commencement, and (vii) were pregnant or lactating were excluded from the study.

This study was approved by the ethics committee of each hospital participating in the study (Pusan National University

Yangsan Hospital 05-2020-018, Busan Paik Hospital 2020-01-022, Kosin University College of Medicine 2020-01-006, Pusan National University Hospital 2020-036-089, Haeundae Paik Hospital 2020-01-020-001, and Dong-A University Hospital 2020-20-116). All procedures followed the ethical standards prescribed by the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1964 and its later versions. This randomized trial was registered with the Clinical Research Information Service of the Korea National Institute of Health (KCT0006120).

2.2. Diagnosis of *H. pylori* infection

Two biopsy specimens were taken from the antrum and corpus of patients during endoscopy. To diagnose *H. pylori* infection, DPO-PCR (Seeplex *H. pylori*-ClAR ACE Detection; Seegene Inc., Seoul, Korea) was performed using DNA extracted from the gastric biopsy specimens. PCR was performed to amplify a portion of the 23S rRNA gene to identify A2142G and/or A2143G mutations associated with clarithromycin resistance.

The success of *H. pylori* eradication was evaluated using the ¹³C-urea breath test (UBiT-IR300; Otsuka Electronics Co. Ltd., Tokyo, Japan) at least 4 weeks after the treatment. All patients swallowed a 100mg tablet of ¹³C-urea (UBiTkit; Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) with 100 mL water after 4 hours of fasting. Two breath samples were collected before and 20 minutes after swallowing the tablet. A cutoff value of ¹³CO₂ < 2.5% was considered successful eradication of *H. pylori*.^[20]

2.3. Eradication regimens

All patients in the CoT group were treated with CoT for 14 days. CoT consisted of rabeprazole 20mg, amoxicillin 1g, clarithromycin 500mg, and metronidazole 500mg twice daily. In the TaT group, patients without A2142G and A2143G point mutations were treated with standard triple therapy for 14 days, and patients with A2142G and/or A2143G point mutations were treated with BQT for 14 days. Standard triple therapy included rabeprazole 20mg, amoxicillin 1g, and clarithromycin 500mg twice daily. BQT consisted of rabeprazole 20mg twice daily, metronidazole 500mg thrice daily, and tetracycline 500mg and bismuth 300mg 4 times daily.

After completing the eradication process, ¹³C-urea breath tests were performed to assess the success rate of *H. pylori* eradication. Patients in whom *H. pylori* eradication failed after the completion of CoT or TaT were recommended to take BQT for 14 days as salvage therapy. In the TaT group, the patients in whom BQT failed as the first-line therapy were recommended to take levofloxacin triple therapy for 14 days. The levofloxacin triple therapy included rabeprazole 20mg and amoxicillin 1g twice daily and levofloxacin 500mg once daily. The eradication success rate of the salvage therapies was also determined using the ¹³C-urea breath test.

2.4. Assessment of drug compliance and treatment-related adverse events

All patients were instructed on how to record adverse events and drug compliance. The patients visited the hospitals and underwent the urea breath test after 4 weeks of finishing the eradication therapies and reported drug compliance and drug-related adverse events. Drug compliance was assessed according to the consumption of the prescribed medication. Noncompliance was defined as the consumption of < 80% of the total medication based on the count of remaining pills. Adverse reactions were graded as mild, moderate, or severe. Mild adverse reactions were defined as > 80% drug compliance and side effects that did not disrupt daily activities. Moderate adverse reactions were defined as < 80% drug compliance and side effects that affected daily activities. Severe adverse reactions were defined as < 50% drug compliance or side effects that limited daily activities.

2.5. Sample size calculation and statistical analysis

Eradication rates obtained in previous studies on CoT and TaT were set at 78.3% and 91.8%, respectively.^[21,22] The minimal number of participants required in each group to obtain statistical power with an α -error of 0.05 and a β error of 0.20 was calculated to be 123. Considering a withdrawal rate of 10%, at least 145 participants in each group were required; therefore, the target sample size was calculated as 290 patients in total.

The intention-to-treat (ITT) and PP analyses were performed to evaluate the eradication rates in the CoT and TaT groups. ITT analysis included all enrolled study population after excluding patients meeting the exclusion criteria. PP analysis excluded the patients who were lost to follow-up or had poor drug compliance (consumed < 80% of the prescribed medications).

Categorical variables were analyzed using the Chi-square test or Fisher exact test, whereas continuous variables were analyzed using Student *t*-test. A *P* value < 0.05 was considered statistically significant. Statistical calculations were performed using the Statistical Package for the Social Sciences version 22.0 for Windows (IBM Corp., Armonk, NY).

3. Results

3.1. Characteristics of the participants

The 290 patients enrolled in this study were randomly assigned to either the CoT (n = 145) or the TaT group (n = 145) between June 2020 and May 2021. Using DPO-PCR test, A2142G, and/or A2143G point mutations were identified in 78 patients (28.6%) who were classified as infected with clarithromycin-resistant *H. pylori*. Among them, 43 (29.7%) patients were assigned to the CoT group and 35 (27.6%) patients were assigned to the TaT group. Clinical characteristics including age, sex, presence of hypertension, and/or diabetic mellitus, and reason of eradication therapy were not significantly different between the 2 groups (Table 1).

The eradication success was not evaluated for 23 patients (11 in the CoT group and 12 in the TaT group) because of follow-up loss after eradication. Two patients in the CoT group and 4 in the TaT group failed to take > 80% of the total medication. Therefore, 290 (145 in the CoT group and 145 in the TaT group) and 261 (132 in the CoT group and 129 in the TaT group) patients were included in ITT and PP analyses, respectively (Fig. 1).

3.2. Eradication rates of *H. pylori*

No significant differences in the eradication rates were observed between the CoT (82.8%) and TaT (85.5%) groups (*P* = .520) based on the ITT analysis. In the subgroup of

patients infected with *H. pylori* without 23S rRNA point mutations, the eradication rates were 88.2% in the CoT group and 84.8% in the TaT group, and the difference was not statistically significant (*P* = .465). For patients infected with *H. pylori* harboring A2142G and/or A2413G mutations, the eradication rate in the CoT group was significantly lower than that in the TaT group (69.8% and 87.5%, respectively, *P* = .050) (Fig. 2).

The eradication rates were 88.6% in the CoT group and 94.6% in the TaT group based on the PP analysis but the difference was not statistically significant (*P* = .084). In the subgroup of patients infected with *H. pylori* without 23S rRNA point mutations, there was no significant difference in the eradication rates between the CoT (93.5%) and TaT (93.6%) groups (*P* = .985). For patients infected with *H. pylori* harboring A2142G and/or A2413G mutations, the CoT group showed significantly lower eradication rate than the TaT group (76.9% and 97.1%, respectively, *P* = .011) (Fig. 3).

3.3. Adverse events

Adverse events including metallic taste, nausea or vomiting, diarrhea, abdominal discomfort or pain, and urticaria were reported in 18.7% (25/134) of the patients in the CoT group and 23.3% (31/133) of the patients in the TaT group (*P* = .351) (Table 2). Among these 56 patients, 2 patients in the CoT group and 4 in the TaT group (4 triple therapy cases) showed severe adverse reactions; the 2 patients in the CoT group reported nausea and/or vomiting, whereas 3 patients in the TaT group reported abdominal pain with diarrhea and 1 patient reported dyspnea and urticaria. These 6 patients were classified as non-compliant because their medication consumption was < 80%. The symptoms of all 6 patients who experienced adverse events disappeared after stopping the eradication medications and taking symptom-control treatment, without hospitalization.

3.4. Salvage therapy and medical costs

BQT was recommended as a salvage regimen for 22 patients in whom the eradication of *H. pylori* infection failed after completing the empirical CoT or TaT. Four of the 22 patients (3 in the CoT group and 1 in the TaT group) refused to receive BQT; therefore, only 18 patients received the second-line BQT for 14 days. Levofloxacin-based triple therapy (14 days) was recommended to 1 patient after the first-line BQT failed. All patients for whom the eradication of *H. pylori* infection failed after CoT or TaT achieved successful eradication with the salvage regimens,

Table 1
Baseline characteristics of patients.

	Concomitant therapy (n = 145)	Tailored therapy (n = 145)	<i>P</i>
Mean age, yrs	59.5	57.1	.079
Sex			.212
Male, n (%)	92 (63.4)	81 (56.3)	
Female, n (%)	53 (36.6)	64 (43.7)	
Smoking, n (%)	36 (24.8)	30 (20.8)	.419
Alcohol, n (%)	50 (53.2)	44 (46.8)	.476
Cause of treatment, n (%)			.299
Peptic ulcer	46 (31.7)	57 (39.6)	
ER for EGC or adenoma	52 (35.9)	39 (27.1)	
MALT lymphoma	1 (0.7)	4 (2.8)	
Gastritis	44 (0.5)	46 (31.7)	

ER = endoscopic resection; EGC = early gastric cancer; MALT = mucosa-associated lymphoid tissue.

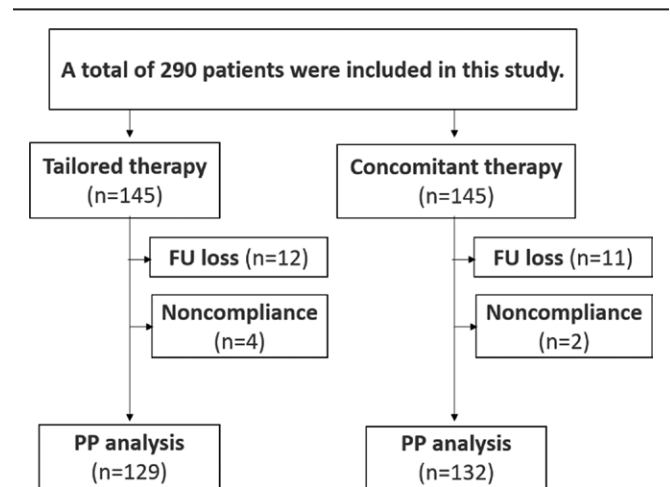


Figure 1. Flowchart of the study.

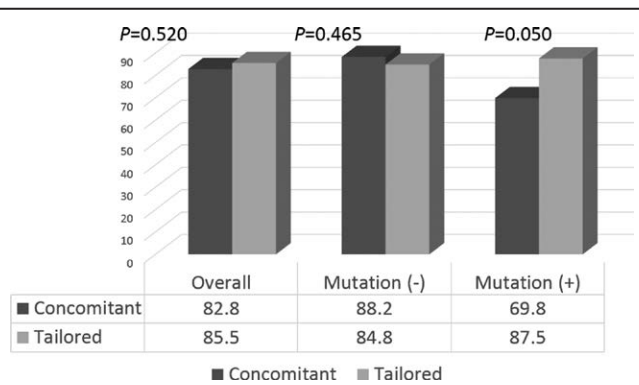


Figure 2. Overall and subgroup eradication rates according to the presence of point mutations as per the intention-to-treat analysis.

except for 2 patients (one in each group) who were lost to follow-up.

The medical cost for each patient treated with CoT was \$413, which included physician consultant fee, gastroscopy with sedation, rapid urease test, eradication medication, and urease breath test. In the TaT group, the medical costs per patient for triple therapy and BQT were \$463 and \$470, respectively. The medical costs for the patients who failed the eradication after CoT, triple therapy, and BQT were \$539, \$589, and \$561, respectively. The average cost per patient for the successful eradication of *H. pylori* was \$424 for CoT and \$468 for TaT (Table 3).

4. Discussion

In this study, the eradication rates of *H. pylori* infection were not significantly different between empirical CoT and DPO-PCR-based TaT according to ITT (82.8% and 85.5%, respectively, $P = .520$) and PP (88.6% and 94.6%, respectively, $P = .084$) analyses. However, the TaT group showed higher eradication rates for *H. pylori* harboring A2142G and/or A2143G point mutations than the empirical CoT group (ITT 87.5% and 69.8%, respectively, $P = .050$; PP 97.1% and 76.9%, respectively, $P = .011$). A recent Korean guideline, revised in 2020, recommends PAM or BQT for patients who are infected with *H. pylori* harboring A2142G and/or A2143G point mutations.^[5,6] Although PAM was considered as the first-line treatment to overcome clarithromycin resistance of *H. pylori*, it did not achieve an acceptable eradication success rate (70–74%).^[18,22] Our findings indicate that BQT should be considered as the first-line treatment regimen for patients infected with *H. pylori* exhibiting clarithromycin resistance. Moreover, PAM and CoT should be discontinued as the first-line treatments for infections caused by clarithromycin-resistant *H. pylori*.

The clarithromycin-resistance rate of *H. pylori* has increased from 21.2% to 45.9% in Korea over the last 15 years.^[9] Several guidelines recommend testing for clarithromycin resistance before considering triple therapy as the first-line treatment in areas with high clarithromycin-resistance rate.^[4–6]

Table 2
Adverse events associated with the 2 therapies.

	Concomitant therapy (n = 134)	Tailored therapy (n = 133)	P
Metallic taste, n (%)	5 (3.7)	7 (5.3)	.546
Nausea, n (%)	6 (4.5)	6 (4.5)	.989
Diarrhea and/or pain, n (%)	11 (8.2)	14 (10.5)	.516
Headache, n (%)	2 (1.5)	2 (1.5)	1.000
Allergy, n (%)	2 (1.5)	2 (1.5)	1.000
Overall, n (%)	25 (18.7)	31 (23.3)	.351

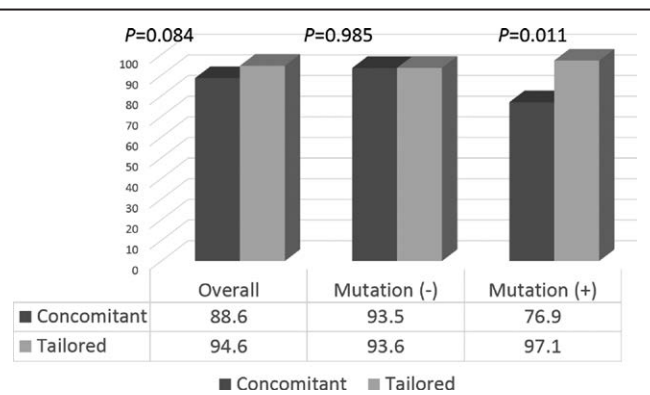


Figure 3. Overall and subgroup eradication rates according to the presence of point mutations, using per-protocol analysis.

Maastricht V/Florence Consensus Report recommends the use of CoT and BQT in areas with high clarithromycin resistance rate (>15%) and low-to-intermediate metronidazole resistance rate (<40%).^[11] A recent culture-based study of the antibiotic resistance profile of *H. pylori* in Korea showed that clarithromycin, metronidazole, and dual resistance rates were 17.8%, 16.2%, and 7.1%, respectively.^[23] A recent Korean nationwide randomized controlled trial reported that the eradication rates of CoT and sequential therapy were 90.6% and 85.0%, respectively, as per PP analyses.^[24] Therefore, CoT and sequential therapy were included as the first-line empirical regimens in the revised Korean guidelines for the treatment of *H. pylori* infection.^[6] However, the metronidazole-resistance rate of *H. pylori* is also currently increasing >40% in Korea.^[9] Maastricht V guideline recommends BQT as the first-line therapy in areas with high dual clarithromycin-metronidazole resistance rate (>15%).^[11] The effectiveness of *H. pylori* eradication regimens is graded as excellent (>95%), good (91–95%), borderline (85–89%), and unacceptable (<85%) based on PP analysis.^[25] In the present study, the eradication rate of CoT was suboptimal (<90%) overall^[26] and unacceptable (76.9%) in patients infected with *H. pylori* harboring A2142G and/or A2143G point mutations.

In addition to the suboptimal eradication rates, in this study, CoT included multiple antibiotics, namely clarithromycin, metronidazole, and amoxicillin, which can lead to antibiotic overuse.^[27] Antibiotic overuse can accelerate the spread of antibiotic-resistant bacteria, not limited to *H. pylori*. Eradication regimens based on antimicrobial susceptibility tests can reach

Table 3
Medical costs involved in the 2 therapies.

	Concomitant therapy (n = 145)		Tailored therapy (n = 145)	
	Success	Fail	Success	Fail
Consultation fee	24	36	24	36
Endoscopy with sedation	254	254	254	254
Rapid urease test	23	23		
DPO-PCR test			78	78
Concomitant therapy	79	79		
Triple therapy			74	74
Bismuth quadruple therapy		81		81
Triple therapy with levofloxacin			46	
Urea breath test	33	66	33	66
Average cost	334	379	389	434
Cost per 1 successful treatment*	424		468	

All values are expressed in US dollars.

*Cost included the first-line therapy and rescue therapy after failure of first-line treatment. DPO-PCR = dual-priming oligonucleotide polymerase chain reaction.

the highest eradication rates.^[28] However, culture-based antimicrobial susceptibility tests are costly, time consuming, and require trained technologists. Therefore, *H. pylori* tissue culture is only available in specialized centers. DPO-PCR test is cost effective and less time consuming compared with culture-based test, and it is widely used to identify mutations in the 23S rRNA gene related to clarithromycin resistance in Korea. Although the average cost of successful eradication in 1 patient was higher for TaT than that for CoT, TaT can increase the eradication rate of clarithromycin-resistant *H. pylori* and reduce the overuse of antibiotics.

Empirical BQT, as the first-line treatment, can be an option to overcome the dual clarithromycin-metronidazole resistance. A recent study comparing the empirical BQT and TaT based on DPO-PCR test showed that a 10-day empirical BQT was more effective and less expensive than TaT.^[29] Another study showed that the eradication rates of 7-day empirical BQT were similar to those of TaT based on DPO-PCR test and that the former was more cost effective.^[30] However, there are only few salvage regimens after BQT failure, and the 4 times daily dosing can decrease the adherence to medication.^[31] To reduce this disadvantage, twice daily administration with the same dose of standard BQT was tested.^[32] Twice daily BQT for 1 week showed an eradication rate similar to that of 4 times daily BQT for 1 week (93.9% and 92.9%, respectively). Twice daily modified BQT (amoxicillin instead of tetracycline) for 14 days was also evaluated, and it exhibited a good eradication rate (93.5% in PP analysis).^[33] Further studies to determine the salvage therapy after BQT failure are needed before considering BQT as a preferred first-line empirical therapy.

In addition to empirical BQT, an empirical treatment consisting of vonoprazan, a potassium competitive acid blocker (P-CAB), can overcome the dual clarithromycin-metronidazole resistance. Japanese studies showed that vonoprazan-based dual or triple therapy had significantly higher eradication rate than that of PPI in patients infected with clarithromycin-resistant *H. pylori*.^[34,35] Stronger and longer-lasting inhibition of gastric acid is considered the reason for the high eradication rate. Vonoprazan is a promising regimen to treat multi-drug resistant bacterial infections, but unfortunately, it is not available in Korea. The eradication rate of triple therapy with tegoprazan, another kind of P-CAB available in Korea, was compared with standard triple therapy with PPI. Tegoprazan 50 mg combined with amoxicillin and clarithromycin did not achieve an acceptable eradication rate.^[36] Authors explained that tegoprazan 50 mg (twice the dose used for gastroesophageal reflux disease) appears insufficient in suppressing the gastric acid and in achieving an acceptable eradication rate. In triple therapy with vonoprazan, the 20 mg dose is 4 times the dose used for gastroesophageal reflux disease.^[35] Further studies using higher doses of tegoprazan or fexuprazan, a new P-CAB drug, are required to evaluate the role of P-CAB in the eradication of clarithromycin-resistant *H. pylori*.^[37]

Our study has several limitations. First, *H. pylori* culture and antimicrobial susceptibility tests were not performed. Nevertheless, in a previous study, the accuracy of DPO-PCR test was determined to be approximately 98% based on comparison of results with those of the culture-based antibiotic resistance test.^[38,39] Second, we did not investigate virulence factors (vacA and cagA). A meta-analysis reported that infection with vacA s1, cagA positive strains is more conducive to eradication therapy than vacA s2, cagA-negative.^[40] Although it would be a limitation, previous report demonstrated that most *H. pylori* strain of Korean patients carry vacA s1 and cagA.^[41] Third, the 6 tertiary hospitals that enrolled patients in this randomized controlled study were located in Busan and Kyungangnam-do, Korea. Nationwide multicenter studies should be performed to overcome this limitation.

In summary, although CoT and TaT showed similar overall eradication rates for *H. pylori*, the eradication rate of CoT was suboptimal, especially for patients infected with 23S rRNA gene point mutation-positive *H. pylori*. Therefore, BQT is a recommended regimen to treat infections with *H. pylori* harboring 23S rRNA point mutations.

Author contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by SJ Kim, SR Jee, MI Park, K Jung, GH Kim, MW Lee, J Lee, JS Jang, and M Koh. Data analysis were performed by SJ Kim. SJ Kim wrote the first draft of the manuscript. SR Jee reviewed edited this manuscript. All authors read and approved the final manuscript

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