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*World J Gastroenterol* 2019 December 14; 25(46): 6704-6798



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**INDEXING/ABSTRACTING**

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2019 edition of Journal Citation Report® cites the 2018 impact factor for WJG as 3.411 (5-year impact factor: 3.579), ranking WJG as 35<sup>th</sup> among 84 journals in gastroenterology and hepatology (quartile in category Q2). CiteScore (2018): 3.43.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: Yan-Liang Zhang

Proofing Production Department Director: Xiang Li

**NAME OF JOURNAL**

*World Journal of Gastroenterology*

**ISSN**

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

**LAUNCH DATE**

October 1, 1995

**FREQUENCY**

Weekly

**EDITORS-IN-CHIEF**

Subrata Ghosh, Andrzej S Tarnawski

**EDITORIAL BOARD MEMBERS**

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

**EDITORIAL OFFICE**

Ze-Mao Gong, Director

**PUBLICATION DATE**

December 14, 2019

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**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

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## Randomized Controlled Trial

# Two-week bismuth-containing quadruple therapy and concomitant therapy are effective first-line treatments for *Helicobacter pylori* eradication: A prospective open-label randomized trial

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**Author contributions:** Kim SY and Chung JW designed the study; Kim SJ, Woo HS, and Chung JW acquired the data; Kim SJ, Woo HS, and Chung JW analyzed the data and interpreted the results; Kim SJ and Chung JW drafted the manuscript; Chung JW, Kim JH, Kim YJ, Kim KO, Kwon KA, and Park DK revised the manuscript for important intellectual content; Kim SJ and Chung JW performed statistical analysis; Chung JW, Kim JH, Kim YJ, Kim KO, Kwon KA, and Park DK contributed to study supervision; all authors critically reviewed and approved the manuscript.

### Institutional review board

**statement:** The Clinical Research Ethics Committee of Gachon University Gil Hospital approved this study.

### Clinical trial registration statement:

This study is registered at Clinical Research Information Service (CRIS). The registration identification number is

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## Abstract

### BACKGROUND

Increasing levels of antibiotic resistance have reduced the *Helicobacter pylori* (*H. pylori*) eradication rates afforded by the standard triple therapy. Thus, 2-wk first-line four-drug regimens must be considered.

### AIM

To analyze the eradication rates of modified bismuth-containing quadruple therapy (mBCQT) and concomitant therapy (CT), the associated adverse events, and compliance.

### METHODS

Patients infected with *H. pylori* were prospectively randomized to receive mBCQT or CT for 2 wk. mBCQT featured a proton pump inhibitor (PPI), bismuth, metronidazole, and tetracycline, taken twice daily. CT included a PPI, clarithromycin, metronidazole, and amoxicillin, taken twice daily. The <sup>13</sup>C-urea breath test was performed no earlier than 4 wk after therapy concluded to confirm eradication. If either the histological or rapid urease test was positive, *H. pylori* infection was diagnosed.

### RESULTS

The demographic characteristics of 68 patients who received mBCQT and 68 who



KCT0001821.

**Informed consent statement:** All involved persons gave their written informed consent prior to study inclusion.

**Conflict-of-interest statement:** The authors declare no conflicts of interest.

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

**CONSORT 2010 statement:** The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

**Open-Access:** This is an open-access article that 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:** Invited Manuscript

**Received:** October 30, 2019

**Peer-review started:** October 30, 2019

**First decision:** November 9, 2019

**Revised:** December 1, 2019

**Accepted:** December 7, 2019

**Article in press:** December 7, 2019

**Published online:** December 14, 2019

**P-Reviewer:** Cheng H, Durazzo M, Fagoonee S, Ierardi E

**S-Editor:** Tang JZ

**L-Editor:** Wang TQ

**E-Editor:** Zhang YL



received CT did not differ significantly. On intention-to-treat analysis, the eradication rate was 88.2% (60/68) in the mBCQT group and 79.4% (54/68) in the CT group ( $P = 0.162$ ). By per-protocol analysis, the respective eradication rates were 98.4% (60/61) and 93.1% (54/58) ( $P = 0.199$ ). More CT than mBCQT patients experienced adverse events [33.8% (23/68) mBCQT *vs* 51.5% (35/58) CT patients, respectively,  $P = 0.037$ ]. All patients showed good compliance [85.3% (58/68) mBCQT *vs* 82.4% (56/68) CT patients,  $P = 0.641$ ].

## CONCLUSION

The *H. pylori* eradication rates of the 2-wk mBCQT and CT regimens are high. Most patients show good compliance, and more CT than mBCQT patients experience adverse events.

**Key words:** *Helicobacter pylori*; Therapy; Bismuth-containing quadruple therapy; Concomitant therapy

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**Core tip:** Both modified bismuth-containing quadruple therapy and concomitant therapy proved to be useful empirical first-line treatment options for *Helicobacter pylori* eradication in an area exhibiting high-level clarithromycin resistance ( $> 15\%$ ).

**Citation:** Kim SJ, Chung JW, Woo HS, Kim SY, Kim JH, Kim YJ, Kim KO, Kwon KA, Park DK. Two-week bismuth-containing quadruple therapy and concomitant therapy are effective first-line treatments for *Helicobacter pylori* eradication: A prospective open-label randomized trial. *World J Gastroenterol* 2019; 25(46): 6790-6798

**URL:** <https://www.wjgnet.com/1007-9327/full/v25/i46/6790.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v25.i46.6790>

## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) infection is the principal cause of peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma. *H. pylori* eradication cures or prevents these diseases<sup>[1]</sup>. However, *H. pylori* is becoming resistant to previously efficacious antibiotic regimens<sup>[2]</sup>. Clarithromycin resistance is increasing worldwide<sup>[2-4]</sup>. The eradication rate afforded by legacy triple therapy (LTT) (the historical first-line treatment for *H. pylori* infection; LTT includes clarithromycin) has declined over the past decade, and has decreased to near 80% or below in some countries of Asia and Europe<sup>[2-4]</sup>. Dual clarithromycin-/metronidazole-resistance of *H. pylori* is also of concern worldwide<sup>[5]</sup>. In South Korea, the dual resistance rate is 9.6%, and it is 19% [95% confidence interval (CI): 0%-39%] in the Eastern Mediterranean Region<sup>[5,6]</sup>.

Thus, many studies have explored the efficacy of first-line alternatives to LTT; these include bismuth quadruple therapy (BQT) and concomitant therapy (CT)<sup>[7-13]</sup>, which feature in the current guidelines<sup>[2,14-16]</sup>. The Maastricht V consensus concluded that, in areas exhibiting high-level ( $> 15\%$ ) clarithromycin resistance but low-level dual clarithromycin/metronidazole resistance ( $< 15\%$ ), BQT or CT should be recommended. In areas exhibiting high-level dual clarithromycin/metronidazole resistance ( $> 15\%$ ), BQT is the recommended first-line treatment (level of evidence: Low; grade and recommendation: High)<sup>[2]</sup>. The revised guidelines for the diagnosis and treatment of *H. pylori* infection in Korea recommend the use of bismuth-containing quadruple therapy (BCQT) if clarithromycin resistance is suspected<sup>[16]</sup>. A meta-analysis found that the eradication rate afforded by CT was slightly higher than that of sequential therapy (ST) [pooled odds ratio (OR) = 1.382,  $P = 0.03$ , intention-to-treat (ITT) analysis; 2.102,  $P = 0.001$ , per-protocol (PP) analysis]<sup>[10]</sup>. However, only a few reports on the efficacy of BCQT and CT have appeared; direct comparisons are rare. Therefore, we performed a prospective, randomized controlled study comparing modified BCQT (mBCQT) and CT as potential first-line treatments for *H. pylori* infection.

## MATERIALS AND METHODS

### Study design and patients

We performed a prospective, open-label, randomized controlled trial in a single tertiary medical center. Patients who underwent endoscopy between February 2016 and August 2017 at Gachon University Gil Hospital, and who received first-of-life diagnoses of peptic ulcer disease, gastritis, gastric polyps, or early gastric cancer, and who then underwent endoscopic mucosal resection, were initially included.

Sample size calculations were performed before the trial began. We assumed, based on previous studies, that the eradication rate of CT was 90%. With little data on BCQT, we assumed an eradication rate of 85% and calculated that a sample size of 60 patients in each of the two groups was necessary ( $\alpha = 0.05$ , power 80%, non-inferiority limit of -10%-10%). The actual sample size was increased to 136 patients to account for patient drop-out.

Of these patients, 136 with confirmed *H. pylori* infections [at least two positive results on either or both of a histological test (Giemsa staining) and the rapid urease test] were enrolled. The 136 patients were randomly divided into two 68-patient groups using a computer-generated block randomization table; the groups received 2-wk treatments with either mBCQT or CT.

The  $^{13}\text{C}$ -urea breath test was performed at 6 wk to 8 wk after antibiotic suspension.

The primary outcome was the eradication rate of *H. pylori*, as determined by ITT and PP analysis. The secondary outcomes were adverse events and compliance.

The study was approved by the Clinical Research Ethics Committee of Gachon University Gil Hospital (approval No. GCIRB2016-006). Written informed consent was obtained from all patients enrolled in the study.

### Confirmation of *H. pylori* infection

When either Giemsa staining or rapid urease test (HP kit; Chong Kun Dang Bio, Seoul, South Korea) was positive upon upper gastrointestinal endoscopy, *H. pylori* infection was diagnosed.

### Eradication of *H. pylori*

The mBCQT regimen featured lansoprazole (Lanston LFDT Tab.) 30 mg, tripotassium bismuth dicitrate 600 mg (Denol Tab.), tetracycline (Tetracycline Cap.) 1000 mg, and metronidazole (Flasinyl Tab.) 500 mg twice daily for 2 wk. CT featured lansoprazole (Lanston LFDT Tab.) 30 mg, clarithromycin (Kloma Tab.) 500 mg, amoxicillin (Amoxapen Cap.) 1000 mg, and metronidazole (Flasinyl® Tab.) 500 mg twice daily for 2 wk.

### Adverse events and compliance

Inadequate drug compliance was defined as ingestion of less than 90% of the total recommended dose. Adverse effects were defined as unexpected symptoms that developed between the commencement and 4 wk after completion of treatment.

### Confirmation of *H. pylori* eradication

The  $^{13}\text{C}$ -urea breath test (UBiT-IR 300/13C-Urea breath test system; Otsuka, Tokyo, Japan) was performed no earlier than 4 wk after treatment concluded, at which time no patient had taken proton pump inhibitors for at least 2 wk. Eradication failure was defined as a positive (delta 2.5) breath test.

### Statistical analysis

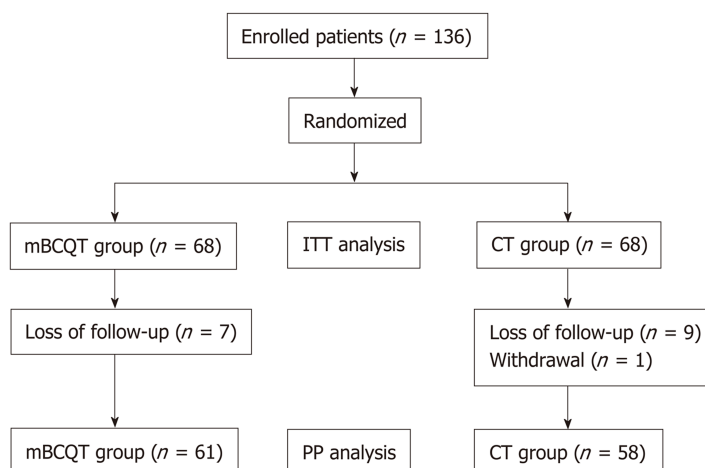
IBM SPSS statistical software (ver. 22.0; IBM Corp, Armonk, NY, United States) was used for all analyses. We employed the  $\chi^2$  test to compare discrete variables and the independent *t*-test to compare continuous variables. We ensured that our sample size had a sufficient non-inferiority margin.

## RESULTS

### Patients

A total of 136 patients were randomly divided into two groups of 68 patients each and compared *via* ITT analysis. Seven mBCQT patients were excluded because of loss to follow-up. Nine CT patients were lost to follow-up and one patient withdrew. The remaining 61 patients in the mBCQT group and 58 in the CT group were compared *via* PP analysis (Figure 1).

The mean age of mBCQT and CT group patients was  $57.37 \pm 11.31$  and  $60.09 \pm 9.93$  years, respectively ( $P = 0.138$ ). The demographic characteristics of the two groups did not differ significantly (Table 1).



**Figure 1 Study flow chart.** mBCQT: Modified bismuth-containing quadruple therapy; CT: Concomitant therapy; ITT: Intention-to-treat; PP: Per-protocol.

### *H. pylori* eradication rates

ITT analysis revealed an eradication rate of 88.2% (60/68) in the mBCQT group and 79.4% (54/68) in the CT group ( $P = 0.162$ ). PP analysis revealed that the eradication rates in the mBCQT group and CT group were 98.4% (60/61) and 93.1% (54/58), respectively ( $P = 0.199$ ) (Table 2). ITT analysis showed that the eradication rates in both the mBCQT and CT groups were close to 80%, but the PP values for both groups were over 90%.

### Adverse events and compliance

Most of the adverse symptoms affected the digestive system. No serious side effect was noted in any patient. The adverse effect rates in the mBCQT group and CT group were 33.8% (23/68) and 51.5% (35/68), respectively, *i.e.*, slightly higher in the CT group ( $P = 0.037$ ). The compliance level was 85.3% in the mBCQT group and 82.4% in the CT group (Table 3).

## DISCUSSION

Both mBCQT and CT proved to be useful empirical first-line treatment options for *H. pylori* eradication. In an area exhibiting high-level clarithromycin resistance ( $> 15\%$ ), both regimens were effective on ITT analysis (mBCQT, 88.2%; CT, 79.4%;  $P = 0.162$ ) and PP analysis (mBCQT, 98.4%; CT, 93.1%;  $P = 0.199$ )<sup>[16,17]</sup>. mBCQT was somewhat, but not significantly, better than CT, by about 8% on ITT analysis and 5% on PP analysis. A large randomized trial performed in Taiwan reported similar results. The cited work used culture to identify clarithromycin-susceptible and -resistant strains, and predicted the efficacy of various drug regimens accordingly. The predicted efficacy of 10-d BQT was greater than that of 10-d CT and 14-d LTT in regions exhibiting high-level clarithromycin resistance, as revealed by multivariate analysis. Similarly, CT was more effective than LTT<sup>[8]</sup>. A prospective study performed in Spain yielded results similar to ours; 10-d BQT (using capsules) and 14-d CT, employed as first-line eradication treatments in an area of high-level clarithromycin resistance, were equally effective<sup>[12]</sup>. A South Korean study found that 10-d PAM-B therapy (rabeprazole 20 mg, amoxicillin 1 g, metronidazole 750 mg, and tripotassium dicitratobismuthate 600 mg twice daily) compared favorably with 14-d CT. The eradication rate of CT was similar to that of the present study, but the PAM-B eradication rate could not be directly compared to the CT data because the regimens differed markedly (ITT analysis, 88.1% *vs* 83.0%,  $P = 0.299$ ; PP analysis, 96.6% *vs* 95.5%,  $P = 0.743$ ). The incidence of adverse events was lower than that in our study (23.0% *vs* 25.2%,  $P = 0.776$ ), perhaps because the duration of 10-d CT of the cited study was shorter than that of our CT<sup>[13]</sup>. The effects of treatment duration on eradication rates and side effects should be studied in future. Both of our regimens featured multiple drugs; compliance remains an issue, but the relatively high eradication rates may reflect good compliance<sup>[18]</sup>. Our mBCQT regimen featured twice-daily dosing, unlike previous studies. Dore *et al*<sup>[19]</sup> reported that daily two- or four-dose second-line regimens afforded similar eradication rates.



**Table 1** Demographic and endoscopic data of the two patient groups

Variable	mBCQT treatment (n = 68)	CT treatment (n = 68)	P value
Age (yr)	57.37 ± 11.31	60.09 ± 9.93	0.138
Gender (male:female)	40:28	32:36	0.169
Height (m)	1.64 ± 0.09	1.63 ± 0.08	0.420
Weight (kg)	64.61 ± 9.23	63.27 ± 9.69	0.409
BMI (kg/m <sup>2</sup> )	24.05 ± 2.88	23.87 ± 2.91	0.704
Smoking	12 (17.6)	14 (20.6)	0.663
Alcohol	18 (26.5)	18 (26.5)	0.999
Gastric and/or duodenal ulcer	27 (39.7)	19 (27.9)	0.147

The values are the mean ± SD, numbers only, or numbers with percentages. mBCQT: Modified bismuth-containing quadruple therapy; CT: Concomitant therapy; BMI: Body mass index.

Also, our mBCQT regimen used a higher dose of tetracycline than other regimens (1000 mg twice daily). A previous Korean study revealed that the extent of tetracycline resistance was relatively low (minimal inhibitory concentration ≥ 2.0 mg/mL, 0%–3.3% of isolates), perhaps attributable to a reduction in tetracycline prescriptions when medical practice and pharmaceutical dispensing were separated in 2000<sup>[6,20,21]</sup>. The tetracycline resistance rate was 0.7% in Spain, 0.5% in the United Kingdom, and 0.5% in Hong Kong; in many countries, the rate was 0%<sup>[22]</sup>. Some studies have explored the efficacy of tetracycline-/amoxicillin-containing regimens. A Korean study comparing a 10-d ST and 14-d PBAT regimen (40 mg pantoprazole, 600 mg bismuth subcitrate, 1 g tetracycline, and 1 g amoxicillin, twice a day) found that ST seemed to be more effective; however, neither regimen afforded ‘excellent’ eradication (over 90%)<sup>[23]</sup>. A Taiwanese study found that quadruple therapy featuring tetracycline and amoxicillin effectively rescued patients in whom triple therapy failed (78% rescue on ITT analysis and 89% on PP analysis). However, apart from our mBCQT regimen, ST featuring tetracycline was associated with relatively low-level eradication<sup>[24]</sup>. These variable results may reflect the fact that both tetracycline and amoxicillin are not very active against *H. pylori*, or that the drugs may act antagonistically<sup>[23]</sup>. In most studies, tetracycline was taken four times daily, but twice-daily regimens are more appropriate and probably also improve compliance; tetracycline is a time-dependent (half-life, 8–10 h) antibiotic agent exhibiting a long post-antibiotic effect. Further studies are needed to explore the adequacy of currently used tetracycline dosages and durations<sup>[23]</sup>.

Although neither of our regimens was associated with serious side effects, the overall incidence of side effects was relatively high. Further efforts to reduce side effects, perhaps *via* addition of probiotics, are essential<sup>[25]</sup>. Previous studies have found that certain probiotics, such as *Lactobacillus* genus and *Bacillus clausii*, reduce gastrointestinal problems and other side effects of eradication therapies<sup>[2,26]</sup>. It has been suggested that the increase in *H. pylori* eradication seen with use of these probiotics is not a direct effect of the probiotics, but a result of the associated reduction in side effects of therapy<sup>[2,26]</sup>.

Although both regimens seemed to be effective first-line therapies, their efficacy in terms of salvage therapy have not been confirmed. The Maastricht V guidelines indicate that, after failure of non-BQT, levofloxacin triple therapy is appropriate<sup>[2]</sup>. However, according to the World Health Organization, quinolone resistance has been reported in over 30% of all regions, and primary levofloxacin resistance in over 15%, except Europe<sup>[5,20,22]</sup>. Therefore, it is necessary to consider rescue regimens containing drugs associated with low *H. pylori* resistance rates.

One study of rifabutin-based therapy reported an eradication rate over 70% (72.7%, 95% CI: 67.3%–77.7%, PP analysis; 71.5%, 95% CI: 66.1%–76.5%, ITT analysis)<sup>[27]</sup>. Although rifabutin-resistant *H. pylori* has been reported, rifabutin-based regimens may be useful as rescue therapies because rifabutin can be used without culture and antibiotic susceptibility testing<sup>[27]</sup>. Also, furazolidone-resistant *H. pylori* is rare; the drug afforded satisfactory eradication rates (relative risk = 1.17, 95% CI: 1.05–1.31)<sup>[28]</sup>. In a multivariate analysis, an increased eradication rate when using high-dose furazolidone was noted (OR = 1.5, 95% CI: 1.3–2.7; *P* < 0.001)<sup>[29]</sup>. According to a recent *in vitro* analysis, there were no strains resistant to rifabutin or furazolidone among multi-drug resistant *H. pylori* (minimum inhibitory concentration < 0.008 and < 0.5 µg/mL, respectively). This suggests that rifabutin- and furazolidone-containing regimens have promise as rescue therapies<sup>[30]</sup>. However, there is controversy over the

**Table 2** Eradication rates afforded by modified bismuth-containing quadruple therapy and concomitant therapy

	Eradication rate		P value
	mBCQT Treatment	CT Treatment	
ITT analysis	88.2 (60/68)	79.4 (54/68)	0.162
PP analysis	98.4 (60/61)	93.1 (54/58)	0.199

mBCQT: Modified bismuth-containing quadruple therapy; CT: Concomitant therapy; ITT: Intention-to-treat; PP: Per-protocol. The values are percentages with numbers.

use of furazolidone-containing regimens because of the drug's potential carcinogenicity. Thus, furazolidone-containing regimens are recommended only in areas with high rates of resistance and for patients who have multiple prior treatment failures and have received patient counseling<sup>[29,31]</sup>.

The limitations of this study included the small number of patients, due to the single-center design. Also, we did not culture *H. pylori*. The strengths of our study include its randomized controlled design and the acceptable therapeutic efficacy in both the mBCQT and CT groups. In conclusion, both mBCQT and CT are promising empirical first-line regimens in an area exhibiting high-level clarithromycin resistance. However, mBCQT is somewhat preferable, considering both side effects and compliance. A large-scale prospective study is required to validate our findings.

Table 3 Adverse events and compliance

	mBCQT treatment (n = 68)	CT treatment (n = 68)	P value
Diarrhea	1.5 (1)	13.2 (9)	0.009
Feces discoloration	5.9 (4)	0 (0)	0.119
Nausea	16.2 (11)	16.2 (11)	0.999
Taste disturbance	5.9 (4)	14.7 (10)	0.090
Miscellaneous	22.1 (15)	20.6 (14)	0.834
Total adverse events	33.8 (23)	51.5 (35)	0.037
Compliance <sup>1</sup>	85.3 (58)	82.4 (56)	0.641

<sup>1</sup>≥ 90% of medications taken. The values are percentages with numbers. mBCQT: Modified bismuth-containing quadruple therapy; CT: Concomitant therapy.

## ARTICLE HIGHLIGHTS

### Research background

*Helicobacter pylori* (*H. pylori*) is becoming resistant to previously efficacious antibiotic regimens, including clarithromycin. The eradication rate afforded by legacy triple therapy (LTT), which includes clarithromycin, has declined over the past decade.

### Research motivation

Many studies have explored the efficacy of first-line alternatives to LTT. However, only a few studies on the efficacy of bismuth-containing quadruple therapy (BCQT) and concomitant therapy (CT) have been conducted.

### Research objectives

To determine the eradication rates of *H. pylori* and compare adverse events and compliance in groups of patients who received modified BCQT (mBCQT) and CT regimens.

### Research methods

We performed a prospective, open-label, randomized controlled trial with 2-week mBCQT and CT regimens.

### Research results

Both mBCQT and CT regimens were effective on intention-to-treat and per-protocol analysis. Most patients showed good compliance. More CT than mBCQT patients experienced adverse events.

### Research conclusions

Both mBCQT and CT proved to be useful empirical first-line treatment options for *H. pylori* eradication in an area exhibiting high-level clarithromycin resistance

### Research perspectives

A large-scale prospective study is required to validate mBCQT and CT as empirical first-line treatment options for *H. pylori* eradication. The effects of treatment duration on eradication rates and side effects should be studied in future.

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