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Bismuth, esomeprazole, metronidazole, and minocycline or tetracycline as a first-line regimen for *Helicobacter pylori* eradication: A randomized controlled trial

Baojun Suo[1], Xueli Tian[2], Hua Zhang[3], Haoping Lu[1], Cailing Li[1], Yuxin Zhang[1], Xinlu Ren[1], Xingyu Yao[1], Liya Zhou[1], Zhiqiang Song[1]

[1]Department of Gastroenterology, Peking University Third Hospital, Beijing 100191, China;
[2]Digestive Disease Research Center of Peking University, Beijing 100191, China;
[3]Research Center of Clinical Epidemiology, Peking University Third Hospital, Beijing 100191, China.

Abstract

Background: Given the general unavailability, common adverse effects, and complicated administration of tetracycline, the clinical application of classic bismuth quadruple therapy (BQT) is greatly limited. Whether minocycline can replace tetracycline for *Helicobacter pylori* (*H. pylori*) eradication is unknown. We aimed to compare the eradication rate, safety, and compliance between minocycline- and tetracycline-containing BQT as first-line regimens.

Methods: This randomized controlled trial was conducted on 434 naïve patients with *H. pylori* infection. The participants were randomly assigned to 14-day minocycline-containing BQT group (bismuth potassium citrate 110 mg q.i.d., esomeprazole 20 mg b.i.d., metronidazole 400 mg q.i.d., and minocycline 100 mg b.i.d.) and tetracycline-containing BQT group (bismuth potassium citrate/esomeprazole/metronidazole with doses same as above and tetracycline 500 mg q.i.d.). Safety and compliance were assessed within 3 days after eradication. Urea breath test was performed at 4–8 weeks after eradication to evaluate outcome. We used a noninferiority test to compare the eradication rates of the two groups. The intergroup differences were evaluated using Pearson chi-squared or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables.

Results: As for the eradication rates of minocycline- and tetracycline-containing BQT, the results of both intention-to-treat (ITT) and per-protocol (PP) analyses showed that the difference rate of lower limit of 95% confidence interval (CI) was >−10.0% (ITT analysis: 181/217 [83.4%] *vs*. 180/217 [82.9%], with a rate difference of 0.5% [−6.9% to 7.9%]; PP analysis: 177/193 [91.7%] *vs*. 176/191 [92.1%], with a rate difference of −0.4% [−5.6% to 6.4%]). Except for dizziness more common (35/215 [16.3%] *vs*. 13/214 [6.1%], $P = 0.001$) in minocycline-containing therapy groups, the incidences of adverse events (75/215 [34.9%] *vs*. 88/214 [41.1%]) and compliance (195/215 [90.7%] *vs*. 192/214 [89.7%]) were similar between the two groups.

Conclusion: The eradication efficacy of minocycline-containing BQT was noninferior to tetracycline-containing BQT as first-line regimen for *H. pylori* eradication with similar safety and compliance.

Trial registration: ClinicalTrials.gov, ChiCTR 1900023646.

Keywords: *Helicobacter pylori*; Minocycline; Tetracycline; Bismuth quadruple therapy

Introduction

Helicobacter pylori (*H. pylori*) infection and its related diseases (gastric cancer, peptic ulcer disease, etc.) are still important global health issues.[1,2] With the rapid and significant increase in antibiotic resistance, the efficacies of commonly used eradication regimens for *H. pylori* infection have decreased significantly.[3,4] Classic bismuth quadruple therapy (BQT), namely bismuth, proton pump inhibitor (PPI), metronidazole, and tetracycline, is currently the most important first-line eradication regimen and recommended by expert consensus and guidelines worldwide.[1,5-8] However, in many areas, tetracycline is difficult to obtain clinically, the incidence of adverse reactions is high, and its use is more complicated, which greatly limits the clinical application of BQT.[9,10] Whether other drugs can be used to replace tetracycline to effectively and conveniently eradicate *H. pylori* infection has become an important focus.

Minocycline, a type of semisynthetic tetracycline,[11,12] has a better bactericidal activity than tetracycline in many pathogenic bacteria.[13] Owing to the higher lipid solubility, minocycline has a higher absorption rate.[14,15] Minocycline has a long half-life and needs to be taken

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Baojun Suo and Xueli Tian contributed equally to this work.

Correspondence to: Zhiqiang Song, Department of Gastroenterology, Peking University Third Hospital, No 49, North Garden Road, Haidian District, Beijing 100191, China
E-Mail: szqinputh@163.com

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orally only once or twice daily, facilitating improvement of patient compliance.[12,15] Significantly, *H. pylori* was sensitive to minocycline in the antibiotic sensitivity testing *in vitro*, and its resistance rate was similar with that of tetracycline.[11,16] Besides, secondary resistance did not easily occur in patients who failed eradication therapy.[17] Taken together, these features and results suggested that minocycline might be a potent alternative to tetracycline for eradication therapy of *H. pylori* infection.

However, the clinical research for eradication of *H. pylori* infection with minocycline-containing regimens is very limited. In the early years, a few case reports of patients with refractory *H. pylori* infection have shown that minocycline in combination with other drugs may have good eradication efficacy.[18,19] Recently, through preliminary prospective cohort studies, we have shown that the quadruple therapy with bismuth potassium citrate, esomeprazole, metronidazole, and minocycline for 14 days achieved satisfactory efficacy for first-line *H. pylori* eradication. The eradication rates in intention-to-treat (ITT) and per-protocol (PP) analyses were 85.5% and 92.6%, respectively.[12] Furthermore, another quadruple therapy with minocycline obtained similar good results (ITT analysis: 87.5% and PP analysis: 92.6%).[11] Both studies also showed that the minocycline-containing BQT had relatively good safety and compliance.[11,12] Therefore, conducting more related research, especially randomized controlled trial (RCT) with classic BQT, to determine the role of minocycline-containing BQT in *H. pylori* eradication is necessary.

The present study aimed to compare the eradication rate, safety, and compliance between 14-day minocycline- and tetracycline-containing BQT as first-line regimens for eradicating *H. pylori* infection.

Methods

Study population

This study was conducted in a tertiary hospital located in Beijing, China between April 2019 and November 2021. The patients with dyspepsia were recruited and considered eligible for enrollment if they were 18–70 years of age and had *H. pylori* infection.

We excluded patients (1) who previously underwent eradication treatment for *H. pylori* infection; (2) who have taken drugs that could influence the study results, including PPIs, potassium-channel acid blockers (P-CABs), H_2 receptor blockers, bismuth, and antibiotics in the last 4 weeks; (3) with gastrointestinal malignancy; (4) with Zollinger-Ellison syndrome; (5) who underwent previous gastric or esophageal surgery; (6) with severe concomitant diseases; (7) with known allergies to any study drug; or (8) who are currently pregnant or lactating or with alcohol abuse.

Ethical Approval

The study protocol was approved by the Medical Ethics Committee of Peking University Third Hospital (No. M2019059) and conducted according to the principles of the *Declaration of Helsinki* and the standards of Good Clinical Practice. All patients voluntarily provided informed consent to participate in the study. The study was registered in the Chinese Clinical Trials Registration (No. ChiCTR1900023646).

Study design

This study was a prospective, open-label, single-center, RCT with the primary objective of verifying whether minocycline-containing BQT is noninferior to tetracycline-containing BQT as the first-line regimen for eradicating *H. pylori* infection. The participants were enrolled based on their eligibility to the inclusion and exclusion criteria. After enrollment, the demographic data and clinical data were collected. The participants were then randomly assigned to one of the two eradication groups in a 1:1 ratio with a parallel arm design. A computer-generated randomization scheme (SAS version 9.1.3; SAS Institute, Cary, NC, USA) was constructed using a block design (block size of four) provided by an independent statistician and was used to determine treatment allocation. The allocation was concealed by using opaque envelopes, which were in turn opened sequentially by the investigator after each patient was deemed eligible and had provided written informed consent. The participants were asked to come back at 1–3 days after eradication to evaluate the safety profile (incidence of adverse events) and compliance (intake of drugs). Participants underwent a ^{13}C-urea breath test (UBT; UCBT Kit; Atom High Tech, Beijing, China) at 4–8 weeks after eradication to evaluate the therapeutic outcomes. Other drugs that could affect the results were prohibited during the study.

Smoking was defined as consumption of >1 pack of cigarettes/week in the previous 6 months. Alcohol drinking was defined as consumption of >50 g of alcohol/day in the previous 6 months. Patients with duodenal and/or gastric ulcer found in upper endoscopy were diagnosed with peptic ulcer disease, while those without ulcer were considered as having nonulcer dyspepsia. Uninvestigated dyspeptic patients included those with dyspeptic symptoms but did not receive upper endoscopy.

Treatment regimens

Minocycline-containing BQT comprised bismuth potassium citrate 110 mg four times daily (before breakfast/lunch/dinner/bedtime), esomeprazole 20 mg twice daily (before breakfast/dinner), metronidazole 400 mg four times daily (after breakfast/lunch/dinner and before bedtime), and minocycline 100 mg twice daily (after breakfast/dinner) for 14 days.

Tetracycline-containing BQT comprised bismuth potassium citrate/esomeprazole/metronidazole with doses same as above and tetracycline 500 mg four times daily (after breakfast/lunch/dinner and before bedtime) for 14 days. Treatment allocation was not blinded.

The study drug information was as follows: bismuth potassium citrate (bismuth potassium citrate capsules

110 mg/capsule; Group Li Zhu Pharmaceutical Factory, Zhuhai, China), esomeprazole (esomeprazole magnesium enteric-coated tablets 20 mg/tablet; AstraZeneca Pharmaceutical Co., Ltd, Wuxi, China), metronidazole (metronidazole tablets 400 mg/tablet; Yabao Pharmaceutical Group Co., Ltd, Yunzhou, China), tetracycline (tetracycline tablets 250 mg/tablet; Hubei Yuancheng Saichuang Technology Co., Ltd, Wuhan, China), and minocycline (minocycline 50 mg/capsule; Wyeth Pharmaceutical Co., Ltd, Suzhou, China).

Safety and compliance

The medical staff in the gastroenterology unit should thoroughly explain the treatment regimens and associated potential adverse events to all enrolled participants. The participants were given both verbal and written instructions about the importance of taking medications regularly and recommended not to stop medication in the event of mild-to-moderate adverse effects. The participants were advised to call the doctor if they had severe side effects. The participants were asked to return at 1–3 days after eradication to determine the incidence of adverse effects and compliance assessment.

The adverse events were determined by asking open-ended questions using patient self-reports and physical examinations and were grouped into mild (no effect on daily routine), moderate (limited effects on daily routine), severe (marked effects on daily routine and medication discontinuation), and serious (death, hospitalization, disability, or required intervention for permanent damage prevention) types.

Compliance was assessed by pill count, which was either considered good (≥80% of pills taken) or poor (<80%). Individuals with poor compliance were not included in the PP analysis.

H. pylori detection

Before enrollment, the status of *H. pylori* infection was determined by one of the two methods: (1) positive in ^{13}C-UBT and (2) positive in both rapid urea test (RUT, HPUT-H102, San Qiang Bio & Che, Fujian, China) and histological Warthin–Starry staining by upper endoscopy. Post-treatment *H. pylori* status was assessed by ^{13}C-UBT at 4–8 weeks after treatment. *H. pylori* infection was considered eradicated if the result of the ^{13}C-UBT was negative.

A gastric biopsy taken from the antrum was subjected to RUT. If the patient was tested positive by RUT, two mucosal biopsy specimens (one each from the antrum and corpus) were obtained for histological Warthin–Starry staining. Two additional specimens (one each from the antrum and corpus) were obtained for culturing and antimicrobial susceptibility testing of *H. pylori*.

PPIs, P-CABs, H_2-receptor blockers, bismuth salts, and antibiotics were discontinued for at least 4 weeks before ^{13}C-UBT was performed. ^{13}C-UBT was performed after overnight fasting. A baseline breath sample was obtained by blowing through a disposable plastic straw into a 20-mL container, and a capsule containing 75-mg ^{13}C-urea was given to patients with 100-mL water. Another breath sample was collected after 30 min. The test was considered positive if the difference between the baseline and 30 min samples exceeded 4.0 parts/1000 of $^{13}CO_2$, as analyzed by using a gas chromatography isotope ratio mass spectrometer (GC-IRMS; GIRMS ZC-202, Wan Yi Sci & Tech, Anhui, China).

H. pylori strain culture and antimicrobial susceptibility testing

H. pylori culture was performed in all the patients receiving upper endoscopy. *H. pylori* strains were isolated and cultured from gastric mucosal samples. *In vitro*, antibiotic resistance was evaluated with the Epsilometer test (AB Biodisk, Stockholm, Sweden).[20] *H. pylori* strains with minimal inhibitory concentrations of >0.125 μg/mL, >0.5 μg/mL, >8 μg/mL, >1 μg/mL, >1 μg/mL, and >8 μg/mL showed resistance to amoxicillin, clarithromycin, metronidazole, levofloxacin, tetracycline, and minocycline, respectively.[16,21]

The endoscopists, pathologists, and technicians who performed RUT, ^{13}C-UBT, Warthin–Starry staining, *H. pylori* strain culture, and antimicrobial susceptibility testing were all blinded to the treatment group allocation.

Statistical analysis

In our previous small-scale pilot trial using tetracycline-containing BQT, the eradication rate in ITT analysis was 86.7%, whereas that of minocycline-containing BQT was 85.5%.[12] Noninferiority test analysis was used by setting the primary endpoint (*H. pylori* eradication rate) noninferiority margin at 10.0% and considering a drop-out rate of 10%, one-sided $\alpha = 0.025$, and $\beta = 0.20$. Altogether, 434 participants with 217 cases per group should be randomized. Differences and 95% confidence intervals (CIs) in the eradication rate between the two groups were calculated. According to the recognized clinical practice of eradication treatment research of *H. pylori* infection worldwide, the difference of eradication efficacy was set to 10% to evaluate the two regimens, so the noninferiority (minocycline- *vs*. tetracycline-containing BQT) would be concluded if the lower limit of the 95% CI was> −10.0% (derived using 10.0% as the noninferiority margin).

The primary outcome variable was the eradication rate with minocycline- and tetracycline-containing BQT using ITT (including the participants who were enrolled in the study) and PP (including the participants who were fully adherent to the protocol and excluding those with poor compliance) analyses. Secondary outcome variables included the incidences of adverse effects and compliance.

Statistical analysis was performed using SPSS for Windows (version 20; IBM Inc., NY, USA). Two-sided $P< 0.05$ was considered to be statistically significant. Categorical variables were described as percentages or frequencies, while continuous variables were described as means ± standard deviation. The eradication rates and 95% CIs

were calculated. The intergroup differences were evaluated using Pearson chi-squared or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. Univariate analysis was performed to evaluate significant predictive variables for eradication of *H. pylori*.

Results

Participants' characteristics

Altogether, 434 participants were randomized into minocycline-containing ($n = 217$) and tetracycline-containing ($n = 217$) BQT groups. All participants were included in ITT analysis. After excluding participants who were lost to follow-up and with trial protocol violation, UBT rejection, adverse drug event intolerance, and poor compliance, the remaining participants were included in PP analysis [Figure 1].

The differences in sex, age, body mass index, diagnosis, smoking, alcohol intake, success rate for *H. pylori* culture, and resistance rate to antibiotics between the two groups were not significant (all $P > 0.05$, Table 1).

Eradication rates

The study's primary objective was to determine the eradication rate of *H. pylori* infection by minocycline-containing BQT and noninferiority to tetracycline-containing BQT. The results of both ITT and PP analyses showed that the rate difference of the lower limit of the 95% CI was>−10.0% (ITT analysis: 83.4% *vs*. 82.9%, with a rate difference of 0.5% [95% CI: −6.9% to 7.9%]; PP analysis: 91.7% *vs*. 92.1%, with a rate difference of −0.4% [95% CI: −5.6% to 6.4%]) [Table 2]. Thus, minocycline-containing BQT was not inferior to tetracycline-containing BQT.

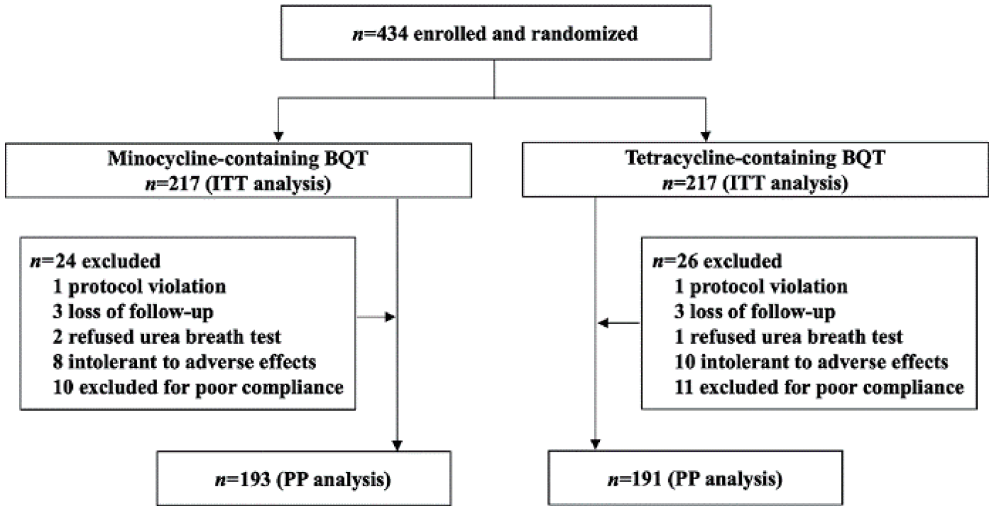

Figure 1: Study flowchart of participants with *H. pylori* infection. ITT: Intention-to-treat; PP: Per-protocol; *H. pylori*: *Helicobacter pylori*; BQT: Bismuth quadruple therapy.

Table 1: Comparison of baseline characteristics of patients with *H. pylori* infection in minocycline- or tetracycline-containing BQT groups.

Baseline characteristics	Minocycline-containing BQT ($n = 217$)	Tetracycline-containing BQT ($n = 217$)	Statistics	*P* values
Gender (male:female)	104:113	109:108	0.230*	0.631
Age (years)	42.2 ± 13.0	41.0 ± 12.9	0.968†	0.334
Body mass index (kg/m^2)	23.0 ± 2.6	23.1 ± 2.6	0.349†	0.727
Smoking (yes:no)	33:184	37:180	0.273*	0.602
Alcohol drinking (yes:no)	34:183	32:185	0.071*	0.789
Diagnosis (PUD:NUD:UID)	16:58:143	14:67:136	0.957*	0.620
H. pylori detection (^{13}C-UBT:upper endoscopy)	143:74	136:81	0.492*	0.483
Successful *H. pylori* culture	63/74 (85.1)	71/81 (87.7)	0.210*	0.647
Amoxicillin resistance	3/63 (4.8)	3/71 (4.2)	<0.001‡	>0.999
Clarithromycin resistance	22/63 (34.9)	24/71 (33.8)	0.019*	0.892
Levofloxacin resistance	23/63 (36.5)	24/71 (33.8)	0.107*	0.743
Metronidazole resistance	38/63 (60.3)	44/71 (62.0)	0.038*	0.844
Tetracycline resistance	3/63 (4.8)	4/71 (5.6)	<0.001‡	>0.999
Minocycline resistance	4/63 (6.3)	5/71 (7.0)	<0.001‡	>0.999

Values were shown as mean ± standard deviation, *n*: *n* or *n*/*N* (%). *Pearson chi-squared test. †Student's *t*-test. ‡Refers to Fisher's exact test. BQT: Bismuth quadruple therapy; NUD: Nonulcer dyspepsia; PUD: Peptic ulcer disease; UBT: Urea breath test; UID: Uninvestigated dyspepsia. *H. pylori*: *Helicobacter pylori*.

Table 2: Comparison of eradication rates of *H. pylori* infection in both BQT groups.

Items	Minocycline-containing BQT	Tetracycline-containing BQT	Rate difference (95% CI)	χ^2	*P* values for difference*
ITT analysis	181/217 (83.4%, 77.6–88.0%)	180/217 (82.9%, 77.1–87.6%)	0.5% (−6.9% to 7.9%)	0.016	0.898
PP analysis	177/193 (91.7%, 86.7–95.0%)	176/191 (92.1%, 87.1–95.4%)	−0.4% (−5.6% to 6.4%)	0.025	0.875

*The *P* values were two-sided and were for comparing the difference of minocycline- and tetracycline-containing group. BQT: Bismuth quadruple therapy; CI: Confidence interval; ITT: Intention-to-treat; PP: Per-protocol.

Safety and compliance

The list and proportion of adverse effects are shown in Table 3. About 75 (34.9%) and 88 (41.1%) patients in minocycline- and tetracycline-containing BQT groups, respectively, had adverse effects. The majority of adverse effects was mild and moderate. Except for dizziness being more common (16.3% *vs*. 6.1%, $P = 0.001$) in minocycline-containing BQT group, the incidence and severity of adverse events between the two groups were similar. No serious adverse effects were reported.

Good compliance was achieved in 195 (90.7%) and 192 (89.7%) in the minocycline- and tetracycline-containing BQT groups, respectively, and the difference was insignificant.

Risk factors for eradication failure

Univariate analysis indicated that the eradication rate was significantly higher in compliant patients than in noncompliant patients in both groups. There was no significant effect of sex, age, body mass index, smoking, alcohol drinking, diagnosis, or antibiotic resistance on the eradication rates in both groups [Table 4].

Discussion

This RCT showed that the minocycline-containing BQT had the similarly satisfactory eradication efficacy, safety, and compliance with the classic tetracycline-containing BQT as the first-line eradication regimen (ITT analysis: 83.4% *vs*. 82.9% and PP analysis: 91.7% *vs*. 92.1%), suggesting that minocycline has a good potential to replace tetracycline for the eradication of *H. pylori* infection. To the best of our knowledge, few head-to-head RCT on the eradication efficacy between the two regimens have been reported.

The reasons why the minocycline-containing BQT can achieve a good eradication rate may include: (1) *H. pylori* strains are sensitive to minocycline and previous studies of *in vitro* drug sensitivity testing proved that the resistance rate of *H. pylori* to minocycline was low.[11,16,19,22] The antibiotic resistance of *H. pylori* strains was investigated in a Japanese study conducted from 1996 to 2008 ($n = 3521$), reporting a very low primary resistance rate to minocycline.[22] The present study and our previous studies revealed a low resistance rate to minocycline (~7%) in China, which is similar to that of tetracycline (5%).[11,16] (2) Minocycline has its

Table 3: Comparison of safety and compliance among patients with *H. pylori* infection in the two groups.

Safety and compliance	Minocycline-containing BQT ($n = 215$)*	Tetracycline-containing BQT ($n = 214$)*	χ^2	*P* values
Patients with adverse reactions	75 (34.9)	88 (41.1)	1.771	0.183
Mild	42 (19.5)	38 (17.8)	2.722	0.256
Moderate	22 (10.2)	32 (15.0)		
Severe	11 (5.1)	18 (8.4)		
Taste distortion	36 (16.7)	46 (21.5)	1.566	0.211
Nausea	43 (20.0)	52 (24.3)	1.150	0.284
Diarrhea	15 (7.0)	20 (9.3)	0.803	0.370
Anorexia	43 (20.0)	50 (23.4)	0.715	0.398
Abdominal pain and discomfort	17 (7.9)	21 (9.8)	0.483	0.487
Fatigue	25 (11.6)	27 (12.6)	0.098	0.754
Headache	12 (5.6)	14 (6.5)	0.174	0.677
Skin rash	6 (2.8)	6 (2.8)	<0.001	0.993
Dizziness	35 (16.3)	13 (6.1)	11.239	0.001
Constipation	6 (2.8)	5 (2.3)	0.089	0.766
Compliance	195 (90.7)	192 (89.7)	0.116	0.733

Values are shown as *n* (%). *Three patients in each group were lost of follow-up. Since one patient in minocycline-containing was lost of follow-up after completing safety and compliance, thus the evaluations can be conducted. The other five patients were lost of follow-up within two weeks, so safety and compliance evaluations cannot be conducted. Therefore, in the minocycline-containing and tetracycline-containing BQT groups, two and three patients were unable to be evaluated for safety and compliance due to lost of follow-up, respectively. BQT: Bismuth quadruple therapy.

Table 4: Univariate analysis showing factors influencing eradication efficacy.

	Minocycline-containing BQT (n = 203)*			Tetracycline-containing BQT (n = 202)*		
Possible factors	**Eradication rate**	χ^2	***P* values**	**Eradication rate**	χ^2	***P* values**
Gender						
Male	86/99 (86.9)	1.052	0.305	90/103 (87.4)	0.648	0.421
Female	95/104 (91.3)			90/99 (90.9)		
Age						
<35 years	54/63 (85.7)	1.169	0.557	60/68 (88.2)	0.766	0.715
35–50 years	74/82 (90.2)			73/80 (91.3)		
>50 years	53/58 (91.4)			47/54 (87.0)		
Body mass index						
<22 kg/m^2	59/71 (83.1)	5.786	0.055	64/75 (85.3)	4.564	0.118
22–25 kg/m^2	78/82 (95.1)			63/72 (87.5)		
>25 kg/m^2	44/50 (88.0)			53/55 (96.4)		
Smoking						
Yes	25/29 (86.2)	0.306	0.528	29/33 (87.9)	0.062	0.764
No	156/174 (89.7)			151/169 (89.3)		
Alcohol drinking						
Yes	30/33 (90.9)	0.124	>0.999	28/31 (90.3)	0.056	>0.999
No	151/170 (88.8)			152/171 (88.9)		
Diagnosis						
PUD	13/14 (92.9)	0.423	0.866	12/13 (92.3)	0.124	>0.999
NUD	47/54 (87.0)			53/60 (88.3)		
UID	121/135 (89.6)			115/129 (89.1)		
Compliance						
Good	177/193 (91.7)	26.309	<0.001	176/191 (92.1)	33.349	<0.001
Poor	4/10 (40.0)			4/11 (36.4)		
Minocycline resistance						
Resistant	2/4 (50.0)	2.444	0.222	–	–	–
Susceptible	51/56 (91.1)			–	–	–
Tetracycline resistance						
Resistant	–	–	–	3/4 (75.0)	0.898	0.373
Susceptible	–	–	–	55/61 (90.2)		
Metronidazole resistance						
Resistant	29/35 (82.9)	6.111	0.063	34/40 (85.0)	1.937	0.235
Susceptible	24/25 (96.0)			24/25 (96.0)		

Values were shown as n (%). *Variable analysis showing factors affecting eradication efficacy was performed in patients who had taken medication and completed the urea breath test. BQT: Bismuth quadruple therapy; NUD: Nonulcer dyspepsia; PUD: Peptic ulcer disease; UID: Uninvestigated dyspepsia; –: Not applicable.

own characteristics and advantages, including a longer half-life (can be taken twice daily and helpful to improve patients' treatment compliance), the better lipid solubility and higher absorption rate (does not easily interact with food and helpful to obtain a better bioavailability), and better safety profile than tetracycline.[13-15] (3) Minocycline is used in combination with full-dose metronidazole (0.4 g four times daily). Although the metronidazole resistance rate is high *in vitro*, the increase in dose and administration frequency can partially or completely overcome the drug resistance and achieve a better eradication effect.[3,9,10,23]

Currently, the studies on minocycline in the treatment of *H. pylori* infection are relatively few. In a systematic review and meta-analysis[24] of studies on semisynthetic tetracycline-containing eradication therapy for *H. pylori* infection published in 2021, only five studies on minocycline-containing quadruple therapies were included, most of which were prospective cohort studies with a small sample size and large-sample RCTs were rare.[11,12,25–27] Three of these studies were reported by our research group, which showed that both the bismuth quadruple therapies (14-day) containing minocycline–metronidazole and minocycline–amoxicillin achieved satisfactory efficacy in eradicating *H. pylori* infection in the first-line, second-line, and refractory eradication treatments of *H. pylori* infection.[11,12,26] The results of a RCT conducted by Zhang *et al*[25] showed that the eradication efficacy of 14-day BQT containing minocycline–metronidazole was not satisfactory (77.1% in ITT analysis and 84.3% in PP analysis), which was possibly associated with a lower metronidazole dose in this group (0.4 g three times daily); while the eradication efficacy of 14-day BQT containing minocycline–amoxicillin was slightly better (85.7% in ITT analysis and 89.5% in PP analysis).

Our study results showed that the incidence of adverse events and compliance were similar between minocycline-containing BQT and tetracycline-containing BQT. The overall safety of minocycline was good, but a few patients (approximately 15–20%) experienced dizziness, which was related to the effect of minocycline on the

vestibule[15]: minocycline can cross the blood–brain barrier better than other tetracyclines due to its lipophilicity; therefore, it may induce nervous system-related side effects. The reaction occurring in most subjects was mild to moderate and tolerable. Only few patients could not tolerate it and had to stop taking medications.

The results of univariate analysis in this study showed that compliance was a risk factor affecting the efficacy of eradication, which was consistent with the findings of previous studies.[28–30] For infectious diseases, whether standardized drug administration is available directly determines the plasma concentration of antibiotics, which is closely related to the eradication efficacy. Antibiotic resistance is recognized as the most important risk factor affecting the efficacy of treatment for *H. pylori* infection.[3,4] Our study results did not show a difference in the eradication rate between the antibiotic resistant and sensitive groups. This might mainly be related to the small number of patients with tetracycline and minocycline resistance and to the effect of full-dose metronidazole to overcome resistance to a certain extent.

The highlight of this study is that the eradication efficacy, safety, and compliance of the two therapies were compared in a standardized manner through an RCT involving a large sample size. The results enriched the optimal selection of clinical eradication regimens, thereby solving the tough issue of eradicating *H. pylori* infection in areas with high antibiotic resistance and tetracycline unavailable.

The limitations of this study included that it was a single-center study and antibiotic susceptibility testing was performed only in some patients due to limited conditions, which might cause selection bias and be worthy of further more comprehensive evaluation and validation in multiple centers in the future. Besides, we should also evaluate the health economic indicators of minocycline, tetracycline, or other antibiotics to eradicate *H. pylori* in the future.

In summary, compared with classic BQT, the eradication efficacy of minocycline-containing BQT as the first-line regimen for eradicating *H. pylori* infection were similar and satisfactory with relatively good compliance and safety. A few patients treated with minocycline experienced dizziness. Poor compliance was the risk factor for treatment failure.

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Conflicts of interest

None.

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