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Efficacy and safety of high-dose esomeprazole and amoxicillin dual therapy *versus* bismuth-containing quadruple therapy for *Helicobacter pylori* infection: a multicenter, randomized controlled clinical trial

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Abstract

Background: A high-dose proton pump inhibitor (PPI)-amoxicillin dual therapy has been investigated for treatment of patients with *Helicobacter pylori* (*H. pylori*) infection. Currently, the efficacy of this dual therapy remains inconclusive, with controversial findings from various single-center clinical trials.

Objectives: To assess the efficacy and safety of high-dose dual therapy (HDDT) compared with the bismuth-containing quadruple therapy (BQT) in treatment-naive patients with *H. pylori* infection.

Design: A multicenter, open-label, randomized controlled clinical trial.

Methods: Three hundred and forty treatment-naïve patients with *H. pylori* infection were prospectively recruited from seven participating hospitals. The enrolled patients were randomized into one of two treatment groups: the HDDT group (esomeprazole, 20 mg four times daily; amoxicillin, 750 mg four times daily) and the BQT group (esomeprazole, 20 mg, twice daily; bismuth potassium citrate, 600 mg, twice daily; amoxicillin, 1 g, twice daily; metronidazole, 400 mg, four times daily). The primary outcome was eradication rate, and secondary outcomes were safety and patient compliance.

Results: The eradication rates in the HDDT group *versus* the BQT group were 86.47% *versus* 87.06% on intention-to-treat (ITT) analysis, 91.88% *versus* 92.50% on modified ITT (MITT) analysis, and 91.77% *versus* 93.04% on per-protocol (PP) analysis, with no significant differences between the two groups. The patient compliance rates in the HDDT group *versus* the BQT group were 97.02% *versus* 95.86%, and no significant difference was found between the two groups. Notably, the HDDT group exhibited significantly lower incidence in the drug-induced adverse events (AEs) compared to the BQT group (16.67% *versus* 47.94%).

Conclusion: HDDT is equally efficacious in eradicating *H. pylori* infection and resulted in good patient compliance and safety compared with BQT. These findings provide evidence in support of HDDT as a first-line treatment for *H. pylori* infection.

Registration: This clinical trial was registered at The Chinese Clinical Trial Registry (trial registration number: ChiCTR2000039096).

Keywords: *Helicobacter pylori*, bismuth-containing quadruple therapy, high-dose dual therapy, eradication therapy, drug-induced adverse event

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Introduction

Helicobacter pylori (*H. pylori*) infection is among the most common chronic bacterial infections, affecting nearly 50% of the population worldwide.[1] In China, the prevalence rate of *H. pylori* infection is approximately 55%.[1] If left untreated, persistent *H. pylori* infection can cause chronic gastritis, gastric mucosa-associated lymphoid tissue lymphoma, peptic ulcer, and even progress into gastric cancer. Thus, eradication treatment is highly recommended for *H. pylori* positive patients.[2–4] However, with the increased use of antibiotics, drug resistance (especially to clarithromycin, metronidazole, and levofloxacin) has been on the rise, resulting in the decreased success of standard proton pump inhibitor (PPI)-based triple therapy for *H. pylori* infection, with a $<80\%$ eradication rate reported in high drug resistance areas.[5] The bismuth-containing quadruple therapy (BQT) has been one of the effective first-line therapies for eradication of *H. pylori* infection, but this treatment has limitations (e.g. low patient compliance due to complex medication). Thus, there remains a need to find a better eradication regimen in the treatment of *H. pylori* infection.

Recently, the dual therapy consisting of high-dose PPI and amoxicillin has been shown to be effective and safe in the eradication treatment of patients with *H. pylori* infection in single-center clinical trials.[6,7] A recent clinical study investigated the efficacy and safety of a dual treatment regimen (esomeprazole, 40 mg, three times daily; amoxicillin, 750 mg, four times daily) and demonstrated high eradication rates of 91.7% on the intention-to-treat (ITT) analysis and 95.7% on the per-protocol (PP) analysis.[6] Similar high efficacy and safety have also been observed in a dual regimen (esomeprazole, 20 mg, four times daily; amoxicillin, 750 mg, four times daily), achieving eradication rates of 87.1% on the ITT analysis, 90.9% on the modified ITT (MITT) analysis, and 92.4% on the PP analysis.[7] However, inconsistent results have been reported with different dual regimens in different populations. For instance, a study in the United States showed that the eradication rate of a dual therapy (esomeprazole, 40 mg, three times daily; amoxicillin, 750 mg, three times daily) was lower than 80%, specifically 72.2% on the ITT analysis and 74.2% on the PP analysis.[8] It should be noted, however, that these inconsistent results were gained from single center trails. Therefore, it is worth conducting multicenter clinical trials to further study the efficacy and safety of dual therapy regimens in the eradication treatment of *H. pylori* infection.

In this study, we conducted a multicenter, randomized controlled clinical trial to assess the efficacy and safety of high-dose dual therapy (HDDT) (esomeprazole, 20 mg four times daily; amoxicillin, 750 mg four times daily) compared with the BQT in treatment-naive patients with *H. pylori* infection. The results of this study provide further scientific evidence in support of HDDT as a first-line treatment for *H. pylori* infection.

Patients and methods

Patients

In this multicenter, randomized controlled clinical trial, 340 treatment-naïve patients infected with *H. pylori* were prospectively enrolled during the period spanning between October 2020 and October 2021. The seven participating hospitals included Chongqing Daping Hospital (Chongqing, China), People's Hospital of Chongqing Banan District (Chongqing, China), The 13th People's Hospital of Chongqing (Chongqing, China), Lanzhou University Second Hospital (Lanzhou, Gansu, China), Yongchuan Hospital Affiliated to Chongqing Medical University (Chongqing, China), Chongqing Red Cross Hospital (Chongqing, China), and Guizhou Provincial People's Hospital (Guiyang, Guizhou, China). During patient enrollment, the following inclusion criteria were used: (1) 18–70 years of age; (2) chronic gastritis diagnosed by gastroscopy; (3) *H. pylori* infection diagnosed by the Rapid Urease Test and ^{13}C-Urea Breath Test (UBT); and (4) treatment-naïve for *H. pylori* eradication therapy. Patients with the following conditions were excluded from this study: (1) use of medications, including PPI, antibiotics, H2 receptor antagonist, bismuth, and probiotics within 4 weeks before initiating the study treatment; (2) female patients during pregnancy and lactation, or those planning pregnancy; (3) taking non-steroidal anti-inflammatory drugs, anticoagulants, or adrenal corticosteroids; (4) alcohol abuse; (5) allergy to the study drugs; (6) serious clinical conditions potentially affecting the evaluation of this study treatment, such as severe liver disease, heart disease, kidney disease, malignant tumor, mental disease, etc.; (7) prior gastric and esophageal surgery; (8) participation in other clinical research within 3 months; and (9)

difficulty in completing the scheduled follow-up visits.

Our study followed the recommendations of the Consolidated Standards of Reporting Trials statement for reporting randomized controlled trials. This study was approved by the Ethics Committee of Chongqing Daping Hospital (Chongqing, China) (Approval number: 2020, No. 105) and was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients. This clinical trial was registered at the Chinese Clinical Trial Registry (www.chictr.org.cn); the trial registration number is ChiCTR2000039096, through which the trial protocol can be accessed.

Study design, treatments, and follow-up

The enrolled patients were randomly and equally allocated into two treatment groups: the HDDT group and the BQT group. The detailed process was as follows: a list of random numbers (blocks with a block number of 4) was generated by the computer software SAS9.2 in advance. Patients from different centers were assigned to a list of random numbers in the order of inclusion after completing the online questionnaire. The demographic and clinical characteristics at baseline were collected from all study subjects prior to initiating treatment. Patients in the HDDT group were treated for 14 days with esomeprazole sodium (AstraZeneca, China) at a dose of 20 mg four times daily in combination with amoxicillin (The United Laboratories Co. Ltd, China) at a dose of 750 mg four times daily. Both drugs were orally administrated, with esomeprazole sodium taken 30 min before three meals and 1 h before going to bed, and amoxicillin was administered 30 min after three meals and 30 min before bed. Patients in the BQT group received a 14-day treatment with esomeprazole sodium (20 mg, twice daily 30 min before breakfast and dinner), bismuth potassium citrate (Livzon Pharmaceutical Group, China) [600 mg (containing 220 mg of bismuth), twice daily 30 min before breakfast and dinner], amoxicillin (1 g, twice daily 30 min after breakfast and dinner), and metronidazole (Kelun Pharmaceutical Co. Ltd., China) (400 mg, four times daily 30 min after three meals and 30 min before bed). During the 14-day treatment period, patients were instructed to report their adherence to the mediations and adverse events (AEs) via phone and WeChat.

Four to eight weeks after completion of the treatment, all patients were required to attend a follow-up visit to assess the efficacy and safety of both treatment groups.

Measurement of primary and secondary outcomes

The primary outcome was efficacy in eradicating *H. pylori*. The eradication of *H. pylori* was assessed using the ^{13}C-UBT assay 4–8 weeks after the treatment, during which a cut-off value of 2.4 was used to determine whether eradication of *H. pylori* was achieved.

Secondary outcomes included medication adherence and safety. Patient diary cards were used to record details of compliance with the prescribed drug regimens, concomitant medications, symptoms, and AEs during the 14-day treatment. One and two weeks after initiating the use of prescribed medications, the patients were followed up through phone call or WeChat, during which details of compliance with the study medications, concomitant drugs, symptoms, and AEs were collected. Medication adherence was determined over the 14-day treatment period using the medication possession ratio (MPR), the proportion of days that a patient had access to the prescribed medications. Good compliance was defined as an MPR of $\geqslant$80%, while poor compliance was considered when an MPR $<$ 80%. AEs were reported by the study patients during the 14-day treatment period. In accordance with their impact on a patient's daily life, AEs were categorized into mild (no impact on the patient's daily life), moderate (there was impact on the patient's daily life that has led to drug discontinuation), and severe (significant impact on the patient's daily life, leading to withdrawal from the medication).

Statistical analysis

Sample size was calculated for the following parameters: *H. pylori* eradication rate of 88%, $\alpha = 0.025$ (one side), $1 - \beta = 0.80$, non-inferiority margin delta $(\delta) = -0.1(-10\%)$, $p = 90\%$, and 95% confidence interval (CI). We estimated 170 cases in each group for comparative analysis of non-inferiority between the two groups. In total, 340 cases, (170 in the HDDT group and 170 in the BQT group) were enrolled in this clinical trial.

Categorical data are expressed as the number of patients and percentage, while continuous data are presented as mean ± standard deviation. Statistical analysis was conducted with SPSS22.0 using the Chi-square test and paired *t*-test. A *p*-value < 0.05 was considered statistically significant between the two groups.

The eradication rate was analyzed with the ITT analysis of all enrolled subjects in each group, the MITT analysis of the patients who took at least one study medication and completed the ^{13}C-UBT assay, and the PP analysis of the patients who completed the treatment with good compliance. Non-inferiority analysis was performed using SAS9.2 software with non-inferiority established when the 95% lower confidence boundary for the difference between the HDDT and BQT groups in eradication rates was >-0.1, with a one-sided alpha level of 0.025. Univariate analysis was performed using Chi-square test to identify significant predictive variables for *H. pylori* eradication in the MITT analysis.

Results

Baseline characteristics of the study patients

A total of 340 treatment-naïve patients with *H. pylori* infection were prospectively enrolled in seven participating centers. Patients were randomly allocated into the HDDT group ($n = 170$) and the BQT group ($n = 170$). Patient enrollment is illustrated in Figure 1. The baseline demographics and clinical characteristics of the study subjects in the two groups are presented in Table 1. There were no significant differences in age, sex, body mass index (BMI), ethnicity, marital status, education levels, and other selected characteristics between the groups (all $p > 0.05$).

Comparison of eradication rates between HDDT and BQT

The eradication rates were compared between the HDDT group and the BQT group using ITT, PP, and MITT analyses. As summarized in Table 2, the ITT analysis revealed eradication rates of 86.47% (147/170; 95% CI 81.27–91.66%) in the HDDT group and 87.06% (148/170; 95% CI 81.96–92.16%) in the BQT group, with no significant difference between the two groups ($p = 0.873$). The MITT analysis indicated that the eradication rates were 91.88% (147/160; 95% CI 87.60–96.15%) in the HDDT group and 92.50% (148/160; 95% CI 88.37–96.63%) in the BQT group, with no significant difference between the two groups ($p = 0.835$). In the PP analysis, the eradication rates were 91.77% (145/158; 95% CI 87.44–96.10%) in the HDDT group and 93.04% (147/158; 95% CI 89.03–97.05%) in the BQT group, with no significant difference between the two groups ($p = 0.671$).

The lower confidence boundary for the difference in eradiation rates was examined between the two groups. As presented in Table 2, the adjusted 95% CI for the difference in the eradication rate was higher than the pre-specified non-inferiority margin of −0.1, and the *p*-values for non-inferiority were 0.0052, 0.0009, and 0.0017 in the ITT, MITT, and PP analyses, respectively. These data (Table 2) indicate that HDDT was not inferior to BQT in the eradication of *H. pylori*.

We also performed univariate analysis of factors in relation to the *H. pylori* eradication rate in the two groups. As shown in Table 3, there was no significant correlation between eradication rates and other variables, including gender, age, BMI, cigarette smoking, alcohol drinking, treatment adherence, gastroscopy diagnosis, previous penicillin exposure, and previous metronidazole exposure (all $p > 0.05$).

Comparison of drug-induced AEs and treatment adherence between HDDT and BQT

Drug-induced AEs were compared between the HDDT and BQT groups. The AEs experienced by the patients during the 14-day treatment mainly included nausea and vomiting, diarrhea, dizziness and headache, change in sense of taste, skin rash, black stool, constipation, decreased appetite, and abdominal pain. As presented in Table 4, overall drug-induced AEs were significantly less frequent in the HDDT group compared to the BQT group (16.67% *versus* 47.93%, $p < 0.01$). After stratifying the drug-induced AEs, the frequencies of nausea and vomiting, dizziness and headache, change in sense of taste, and black stool were significantly lower in the HDDT group compared to the BQT group (all $p < 0.05$) (Table 4). There were no significant differences in the frequencies of diarrhea, skin rash, constipation, decreased appetite, and abdominal pain between the groups (all $p > 0.05$). Three patients withdrew from the study in the BQT group due to

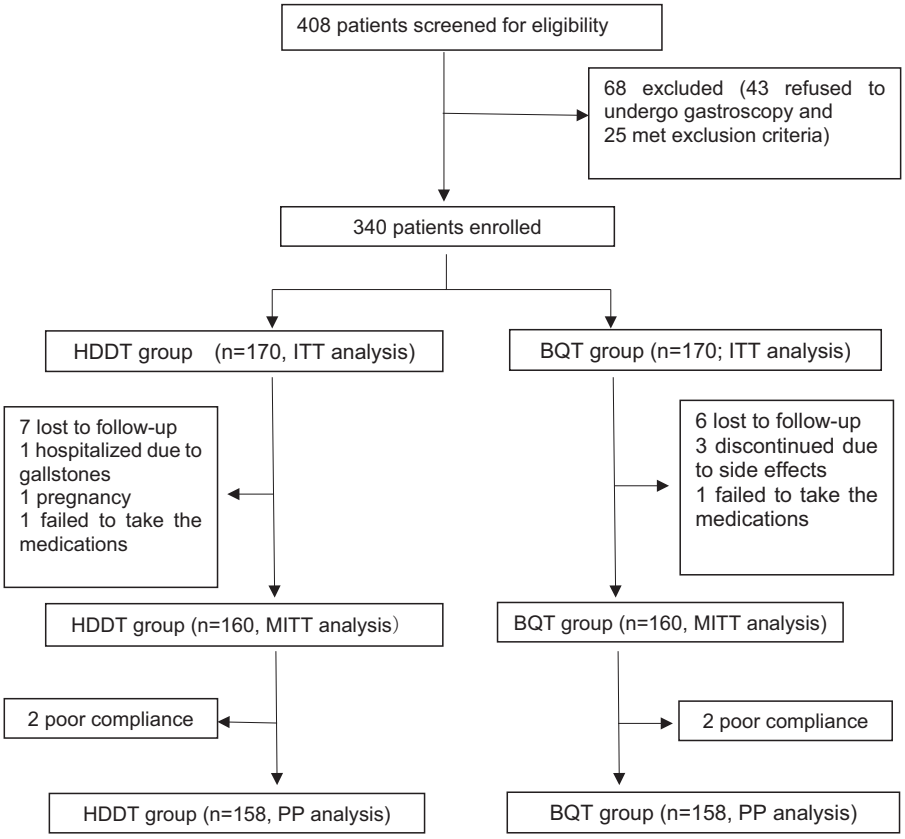

Figure 1. Schematic illustration of patient enrollment and study design. A total of 408 patients who were infected with *H. pylori* were evaluated for their eligibility to enroll in this study. After excluding 68 patients, including 43 who refused to undergo gastroscopy and 25 who were ineligible, 340 patients were enrolled and randomly allocated to the HDDT group ($n = 170$, ITT population) and the BQT group ($n = 170$, ITT population). The MITT population in the HDDT group ($n = 160$) and the BQT group ($n = 160$), and the PP population in the HDDT group ($n = 158$) and the BQT group ($n = 158$) are shown.
ITT, intention-to-treat; MITT, modified intention-to-treat; PP, per-protocol.

intolerable drug-induced nausea and vomiting, whereas none of the patients withdrew from study in the HDDT group (Figure 1).

Comparative analysis revealed good treatment adherence, and no significant difference was found between the HDDT and the BQT groups (97.02% *versus* 95.86%, $p > 0.05$) (Table 4).

Discussion

This multicenter clinical study investigating the efficacy and safety of HDDT *versus* BQT for eradication of *H. pylori* infection in treatment-naive patients resulted in the following major findings: (1) HDDT (esomeprazole, 20 mg, four times daily; amoxicillin, 750 mg, four times daily) was highly effective in eradicating *H. pylori* infection with no inferiority compared to BQT (esomeprazole, 20 mg, twice daily; bismuth potassium citrate (600 mg, twice daily; amoxicillin 1 g, twice daily; metronidazole 400 mg, four times daily), (2) the HDDT group had significantly lower incidence of drug-induced AEs compared to the BQT group, and (3) patients showed good compliance to HDDT or BQT, with no significant difference between the two groups. Collectively, this study supports HDDT as an alternative first-line treatment for *H. pylori* infection.

In this study, HDDT achieved high eradiation rates of 86.47% on ITT analysis, 91.88% on MITT analysis, and 91.77% on PP analysis, and these findings are consistent with the results from a previous single-center trial (ITT: 87.9%; MITT: 91.1%; and PP: 91.1%).[9] Recently, Guan and colleagues performed an open-label, multicenter randomized controlled trial to compare

Table 1. Baseline characteristics of the study patients in the HDDT and the BQT groups.

Characteristics	HDDT group ($n = 170$)	BQT group ($n = 170$)	p-Value
Gender (male:female)	69:101	78:92	0.325
Age (years)	44.80 ± 12.35	45.12 ± 12.34	0.809
BMI (kg/m^2)	23.20 ± 3.14	23.20 ± 2.86	0.884
Ethnicity (Han:Non-Han)	168:2	168:2	1
Living area (urban:rural)	121:49	122:48	0.904
Marital status (married:unmarried)	151:19	146:24	0.415
Education level (below tertiary education:tertiary education and above)	92:78	96:74	0.663
Sources of drinking water (safe and clean:unknown)	166:4	167:3	0.703
Splitting a family-style meal (yes:no)	20:150	23:147	0.624
Number of family members ($\leqslant 3$:>3)	103:67	95:75	0.379
House size (m^2)	104.52 ± 55.72	105.27 ± 36.30	0.969
Cigarette smoking (yes:no)	23:147	27:143	0.540
Alcohol drinking (yes:no)	62:108	66:104	0.654
Previous Penicillin exposure (yes:no)	106:64	95:75	0.225
Previous metronidazole exposure (yes:no)	34:136	32:138	0.784
Gastrointestinal symptoms before treatment (yes:no)	48:122	44:126	0.625
Family history of gastric cancer (yes:no)	7:163	6:164	0.777
Gastroscopy diagnosis (non-atrophic gastritis:atrophic gastritis)	129:41	116:54	0.116

Categorical data are expressed as the number of patients and percentage in parentheses; continuous data are presented as mean ± standard deviation.
BMI, Body mass index; BQT, bismuth-containing quadruple therapy group; HDDT, high-dose esomeprazole and amoxicillin dual therapy group.

HDDT with BQT in treatment-naive patients with *H. pylori* infection, and the eradication rates on ITT and PP analyses were 89.4% and 90.6%, respectively.[10] These recent studies, including ours, provide evidence in support of HDDT as a first-line treatment for *H. pylori* infection.[11–13] The high eradication success rate of HDDT in Chinese patients is mainly attributed to the following factors: (1) in China, the rate of resistance to amoxicillin was as low as 1%[14]; (2) amoxicillin administered four times daily allows higher than the minimum inhibition concentration (MIC) dose[15]; (3) PPI administered four times daily may diminish the potential influence of CYP2C19 genetic polymorphisms in patients with *H. pylori* infection, which is especially beneficial for patient populations with a fast metabolism.[16,17] In addition, higher dosing frequency of the same accumulative PPI dose (i.e. four times daily) has been associated with longer lasting anti-acidic effects[18]; and (4) when the gastric pH value is higher than 6, *H. pylori* has been shown to be more sensitive to antibiotics, improving the stability of amoxicillin and decreasing the MIC, therefore leading to

Table 2. Comparison of eradication rates between the two groups.

	HDDT group	BQT group	Adjusted 95% CI for difference	*p*-Value for non-inferiority	*p*-Value for difference
ITT	86.47% (147/170)	87.06% (148/170)	−0.59%	0.0052	0.873
(95% CI)	(81.27%–91.66%)	(81.96%–92.16%)	(−7.79%–6.62%)		
MITT	91.88% (147/160)	92.50% (148/160)	−0.63%	0.0009	0.835
(95% CI)	(87.60%–96.15%)	(88.37%–96.63%)	(−6.51%–5.26%)		
PP	91.77% (145/158)	93.04% (147/158)	−1.27%	0.0017	0.671
(95% CI)	(87.44%–96.10%)	(89.03%–97.05%)	(−7.11%–4.57%)		

BQT, bismuth-containing quadruple therapy; CI, confidence interval; HDDT, high-dose esomeprazole and amoxicillin dual therapy; ITT, intention-to-treat; MITT, modified intention-to-treat; PP, per-protocol.

better efficacy in the eradication of *H. pylori* infection.[19–21]

Based upon the aforementioned studies, it is critically important to maintain high intragastric pH in HDDT therapy. An increased frequency of PPI can effectively inhibit gastric acid secretion, thereby enhancing the efficacy of amoxicillin. However, previous studies from the United States reported the eradication rate of 72.2% by ITT and 74.2% by PP,[8] which were lower than that (ITT, 86.47%; PP, 91.77%) in our study, as well as that (ITT, 87.9%; PP, 91.1%) in a previous single-center trial.[9] The distribution of CYP2C19 genotypes in different populations may contribute to inconsistent results among different studies. We propose that these inconsistencies may be attributed to, at least in part, an inadequate frequency of PPIs. Although high efficacy can be achieved by an increased frequency of drug administration, up to four times a day, the PPIs used in most previous studies were second-generation PPIs (rabeprazole, esomeprazole). It is currently uncertain whether the first-generation PPIs, such as omeprazole and lansoprazole, could have similarly high efficacy. Additionally, taking multiple doses (3–4 times daily) of a medication is associated with an increase in drug regimen complexity and a decrease in patient treatment compliance. Recently, a novel acid blocker, vonoprazan, was shown to be more effective when administrated less frequently than traditional PPIs in suppressing gastric acidity.[22] Notably, a 7-day treatment regimen consisting of vonoprazan (20 mg) plus amoxicillin (750 mg) twice daily achieved a satisfactory eradication rate (ITT: 84.5%, PP: 87.1%).[23] Therefore, it is worthwhile to investigate whether vonoprazan could replace PPI in future studies of HDDT.

The high eradication rate achieved by the use of HDDT may be attributed to generally low resistance to amoxicillin in these regions, although CYP2C19 genetic polymorphisms in different populations can affect *H. pylori* eradication.[8] In the Americas, the resistance rate for amoxicillin was relatively high, accounting for approximately 10%,[14] and this could have reduced the efficacy of HDDT in the eradication of *H. pylori*. In line with the above findings, the eradication rate of HDDT for the amoxicillin resistant population was only 50% (5/10), and further analysis suggested that amoxicillin resistance was an independent risk factor for failure of *H. pylori* eradication after treatment with HDDT (OR: 11.797).[7] Therefore, physicians need to take the prevalence of regional amoxicillin resistance into account prior to using HDDT for *H. pylori* eradication.

In addition to maintaining high intragastric pH in HDDT and considering regional prevalence of amoxicillin resistance, a 14-day course of HDDT was superior to a 10-day course of HDDT for treatment of *H. pylori* infection (eradication rate, 89.7% *versus* 79.4%).[24] The Maastricht V/Florence Consensus Report among all others recommends an extension of the course of the BQT regimen to 14 days to achieve clinical effectiveness, unless a 10-day course has been demonstrated to be clinically effective in the region.[2–4] Nevertheless, the eradication rate of a 10-day

Table 3. Univariate analysis of factors associated with *H. pylori* eradication rate between the two groups.

Variables	HDDT group ($n = 160$)		BQT group ($n = 160$)	
	Eradication rate	*p*	Eradication rate	*p*
Gender				
Male	59/64	0.906	67/72	0.809
Female	88/96		81/88	
Age (years)				
⩽50	85/93	0.795	93/100	1
>50	62/67		55/60	
BMI (kg/m^2)				
<22	52/56	0.119	59/61	0.212
22–25	54/59		55/62	
>25	41/45		34/37	
Cigarette smoking				
Yes	21/22	0.809	21/24	0.556
No	126/138		127/136	
Alcohol drinking				
Yes	91/100	0.823	93/100	1
No	56/60		55/60	
Treatment adherence				
Good	145/158	1	148/159	0.106
Poor	2/2		0/1	
Gastroscopy diagnosis				
Non-atrophic gastritis	110/121	0.652	99/108	0.798
Atrophic gastritis	37/39		49/52	
Previous Penicillin exposure				
No	57/61	0.786	64/71	0.312
Yes	90/99		84/89	
Previous metronidazole exposure				
No	120/128	0.169	121/131	1
Yes	27/32		27/29	

BMI, Body mass index; BQT, bismuth-containing quadruple therapy; HDDT, high-dose esomeprazole and amoxicillin dual therapy.

Table 4. Comparison of drug-induced AEs and treatment adherence between the two groups.

	HDDT group ($n=168$)	BQT group ($n=169$)	p-Value
AEs	28 (16.67%)	81 (47.93%)	<0.01
Mild	27 (16.07%)	74 (43.79%)	0.296
Moderate	0 (0%)	4 (2.37%)	
Severe	1 (0.59%)	3 (1.78%)	
Types of AEs			
Nausea and vomiting	3 (1.79%)	27 (15.98%)	<0.01
Diarrhea	6 (3.57)	8 (4.73%)	0.593
Dizziness and headache	11 (6.55%)	25 (14.79%)	0.014
Change in sense of taste	0 (0%)	17 (10.06%)	<0.01
Skin rash	6 (3.57%)	2 (1.18%)	0.279
Black stool	0 (0%)	12 (7.10%)	0.01
Constipation	0 (0%)	2 (1.18%)	0.481
Decreased appetite	0 (0%)	1 (0.59%)	1
Abdominal pain	4 (2.38%)	5 (2.96%)	1
Treatment adherence	163 (97.02%)	162 (95.86%)	0.564

AEs, adverse events; BQT, bismuth-containing quadruple therapy; HDDT, high-dose esomeprazole and amoxicillin dual therapy.

course of BQT therapy in China was only 76.7%,[25] and this could be due to the relatively high metronidazole resistance rate (77%) in China.[14] A 14-day course of full- dose metronidazole was thus adopted to overcome resistance and in turn ensure the efficacy of BQT.[2–4] However, this regimen has been associated with a high rate of AEs (47.93%) potentially attributable to the increased dose and duration of the treatment. It would be worthwhile to further investigate whether drug-induced AEs could be minimized through reducing the dose and duration while achieving *H. pylori* eradication.

BQT is highly recommended by major guidelines as a first-line treatment for eradication of *H. pylori* infection despite its limitations, such as low patient compliance among others. Comparison of eradication rates of HDDT with BQT in this study showed that the efficacy of HDDT is not inferior to that of the BQT (ITT: $p=0.0052$; MITT: $p=0.0009$; and PP: $p=0.0017$). Furthermore, both HDDT and BQT in this study achieved good compliance rates (97.60% *versus* 96.42%) with no significant difference. It is worth noting that the incidence of AEs was significantly lower in the HDDT group than that of the BQT group.

This study has some limitations that should be noted. First, we did not examine the effects of drug resistance to antibiotics and CYP2C19 polymorphisms on the efficacy of the treatments. However, according to our previous studies, drug resistance to antibiotics and the CYP2C19 genotypes did not affect the efficacy of the HDDT.[9] Secondly, amoxicillin was present in both treatments, which may not be applicable to individuals who are allergic or have a high resistance to amoxicillin.

In summary, this multicenter clinical trial demonstrated that HDDT is equally efficacious and not inferior to BQT for eradicating *H. pylori*

infection, and that HDDT has a higher safety profile in Chinese treatment-naïve patients. As such, the findings presented here provide evidence supporting the recommendation that HDDT can be used as a first-line treatment for *H. pylori* infection.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Chongqing Daping Hospital (Chongqing, China) approved this study (Approval number: 2020, No. 105).

Written informed consent to participate was obtained from all participants.

Consent for publication

Not applicable.

Author contribution(s)

Hao Mei: Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Visualization; Writing – original draft.

Yan Guo: Data curation; Investigation; Methodology; Project administration.

Jing-Tao Zhao: Data curation; Investigation; Methodology; Project administration.

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Chun-Hui Lan: Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data supporting the findings of this study are available within the article and supplementary material.

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Supplemental material

Supplemental material for this article is available online.

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