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New single capsule of bismuth, metronidazole and tetracycline given with omeprazole versus quadruple therapy consisting of bismuth, omeprazole, amoxicillin and clarithromycin for eradication of *Helicobacter pylori* in duodenal ulcer patients: a Chinese prospective, randomized, multicentre trial

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Objectives: To assess the efficacy and safety of omeprazole given with the new single capsule of bismuth, metronidazole and tetracycline (OBMT) compared with quadruple treatment consisting of omeprazole, bismuth, amoxicillin and clarithromycin (OBAC) for *Helicobacter pylori* eradication in duodenal ulcer patients.

Methods: This single-blind, randomized multicentre trial was conducted in 10 tertiary hospitals in China between January 2013 and April 2014. Patients were randomized to receive 10 days of OBMT therapy or 10 days of OBAC therapy. Our primary outcome was the *H. pylori* eradication rate, confirmed by negative [13C]urea breath tests 20–25 days after the end of omeprazole maintenance. Antibiotic resistance was determined by Etest. This study is registered with ClinicalTrials.gov, number ChiCTR-TRC-13003143.

Results: One hundred and ninety-two patients received OBMT therapy and 192 received OBAC therapy. There was no significant difference between the eradication rates achieved by OBMT and OBAC in either the ITT analysis (86.46% versus 87.50%, $P = 0.762$) or the PP analysis (94.58% versus 93.06%, $P = 0.563$). The efficacies of OBMT and OBAC were not affected by metronidazole or clarithromycin resistance. Treatment-emergent adverse events (TEAEs) for both treatments were similar; gastrointestinal and CNS symptoms were the most commonly reported.

Conclusions: The new single-capsule OBMT quadruple therapy is as effective and well tolerated as the widely used OBAC therapy for treatment of *H. pylori* in clinical practice in China. In addition, this OBMT therapy largely overcomes *H. pylori* metronidazole and clarithromycin resistance.

Introduction

Helicobacter pylori infection is a public health problem affecting almost 50% of the people in the world[1] and is the major cause of many gastroduodenal disorders, such as chronic gastritis, peptic ulcer disease, gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma.[2–4] *H. pylori* strains demonstrate high resistance to metronidazole and clarithromycin in most areas of China,[5–7] which contributes to the low eradication rate using standard triple therapy.[8–10] Bismuth-containing therapy is

recommended in regions with high resistance to clarithromycin or metronidazole because the addition of bismuth to other antibiotic regimens has been proved to improve *H. pylori* eradication.[4,11–13] At present, bismuth-containing quadruple therapy seems to be a reliable regimen and achieves a high rate of *H. pylori* eradication, and is recommended by the fourth Chinese *H. pylori* consensus report, Maastricht V and other recent guidelines.[14–16]

Bismuth-containing quadruple therapy with bismuth, metronidazole and tetracycline plus a proton pump inhibitor (PPI) is also a recommended therapy with a desired *H. pylori* eradication rate,[8,12,17] yet the complex administration protocol may hamper its acceptability for general use. The single (three-in-one) capsule, which includes bismuth subcitrate potassium, metronidazole and tetracycline, has been developed in an attempt to improve patient convenience and is given with omeprazole as quadruple therapy (OBMT) for *H. pylori* eradication abroad. Studies reported that this type of capsule achieved eradication rates higher than 85%, was well tolerated and overcame *H. pylori* metronidazole and clarithromycin resistance.[18–21]

At present, no one to our knowledge has reported whether the single-capsule bismuth-containing plus omeprazole quadruple therapy is efficacious and well tolerated for *H. pylori* eradication in China. Therefore, we aimed to evaluate the efficacy and safety of the single-capsule bismuth-containing quadruple therapy for 10 days versus bismuth subcitrate potassium, omeprazole, amoxicillin and clarithromycin (OBAC) for 10 days for *H. pylori* eradication.

Methods

This study is registered with ClinicalTrials.gov, number ChiCTR-TRC-13003143.

Participants

Our trial was done at 10 tertiary hospitals in China, between January 2013 and April 2014. It was a randomized, single-blind (investigators unaware of study drug allocation), positive parallel controlled, multicentre clinical trial.

Eligible patients were aged 18–66 years with confirmed *H. pylori* [positive [13C]urea breath and rapid urease tests] and active duodenal ulcer documented by endoscopy ($\geq$3 and $\leq$15 mm). Patients were excluded if they had previously used antibiotics to eradicate adequately recorded infection with *H. pylori*, continuously used antibiotics or bismuth compounds (more than 3 times per week, 1 month before screening), received anti-ulcer drugs (during the 2 weeks before screening), had known contraindications to study drugs, non-steroidal anti-inflammatory drugs, anticoagulants or platelet aggregation inhibitors, or abused drugs or alcohol. Patients were excluded if they had surgery of the upper gastrointestinal tract or oesophagus lesions, combined with gastric ulcer, Zollinger-Ellison syndrome, dysphagia, history of malignancy, severe concomitant cardiovascular, respiratory, haematological, renal, hepatic or neurological diseases, or clinically significant laboratory abnormalities at baseline. Women were excluded if they were pregnant, lactating or without contraceptives and of reproductive age. In addition to the above, the investigator decided they were not suitable for the clinical trial.

Procedure

At baseline endoscopy, five biopsies were taken: one antral biopsy for rapid urease test, one antral and one body biopsy for histology and one antral and one body biopsy for culture and testing for antibiotic resistance at a central laboratory. Strain antibiotic resistance was judged by Etest (AB Biodisk, Solna, Sweden) as follows: clarithromycin resistant if MIC $\geq$1.0 mg/L, clarithromycin intermediate if 0.25 < MIC < 1.0 mg/L, clarithromycin susceptible if MIC $\leq$0.25 mg/L and metronidazole resistant if MIC >8.0 mg/L.

Eligible patients were randomly assigned to receive either 10 days OBMT or 10 days OBAC therapy. The OBMT therapy consisted of three-in-one capsules (Sichuan Baili Pharmaceutical Co., Chengdu, Sichuan, China) containing 140 mg of bismuth biskalcitrate (equivalent to 40 mg of bismuth trioxide), 125 mg of metronidazole and 125 mg of tetracycline hydrochloride, taken four times daily (after meals and at bedtime), plus one 20 mg omeprazole capsule (AstraZeneca, Wuxi, Jiangsu, China), taken twice daily (after morning and evening meals). The OBAC therapy consisted of one 20 mg omeprazole capsule, two 300 mg bismuth potassium citrate capsules (Livzon Medicine Group Co., Zhuhai, Guangdong, China), two 250 mg clarithromycin capsules (Abbot, Shanghai, China) and two 500 mg amoxicillin capsules (Zhuhai United Laboratories Co., Zhuhai, Guangdong, China), taken twice daily (before morning and evening meals). After the 10-day course of *H. pylori* eradication therapy, patients would receive 20 mg omeprazole maintenance treatment daily (before morning meal) for 2 weeks. Patients were told to refrain from drinking alcohol during the entire treatment period and for 48 h after the last dose and were told not to take other antacids and antibiotics etc.

Patients returned for the first follow-up visit within 4 days after the end of *H. pylori* eradication therapy. During the first follow-up visit, patients returned for dispensing of maintenance treatment, recording of treatment-emergent adverse events (TEAEs) and drug combination, and evaluation of compliance. Patients returned for the second follow-up visit 45–50 days after the start of *H. pylori* eradication therapy. During the second follow-up visit, a [13C]urea breath test was performed and TEAEs and drug combination were recorded. The patients who did not complete their full course of therapy also returned for a [13C]urea breath test. In addition, all patients with a positive breath test at the second follow-up visit underwent repeat upper endoscopy with biopsies for antibiotic susceptibility testing. Acceptable compliance was defined as consumption $\geq$80% of the study medications.

The primary outcome was the *H. pylori* eradication rate of each therapy, established by negative [13C]urea breath tests. The secondary outcomes were the eradication rates of antibiotic resistance and the safety and tolerability of the treatments.

Ethics

The study protocol was approved by Ethics Committees of all participating centres (approval reference numbers: #045/2012). All patients provided written informed consent before enrolment.

Statistical analysis

The sample size calculation was based on results from a published pooled-data analysis,[18] Δ (non-inferiority margin) of -10%, $\beta = 0.20$ and $\alpha = 0.025$ (one-sided). One hundred and sixty-nine patients in each group were needed to show non-inferiority of OBMT versus OBAC on the basis of the primary outcome. At least 200 patients were randomly assigned to each group, accounting for a 20% withdrawal rate. Statistical analysis was performed by SPSS software (version 11.0, Chicago, IL, USA). Differences between the two therapies were evaluated using the Student's *t*-test for continuous variables and Pearson's χ^2 or Fisher's exact test for categorical variables. A *P* value <0.05 was considered statistically significant.

Results

Patients

Figure 1 shows the trial flowchart. A total of 384 patients were recruited from 10 tertiary hospitals in China, including 233 men and 151 women. One hundred and ninety-two patients were randomly

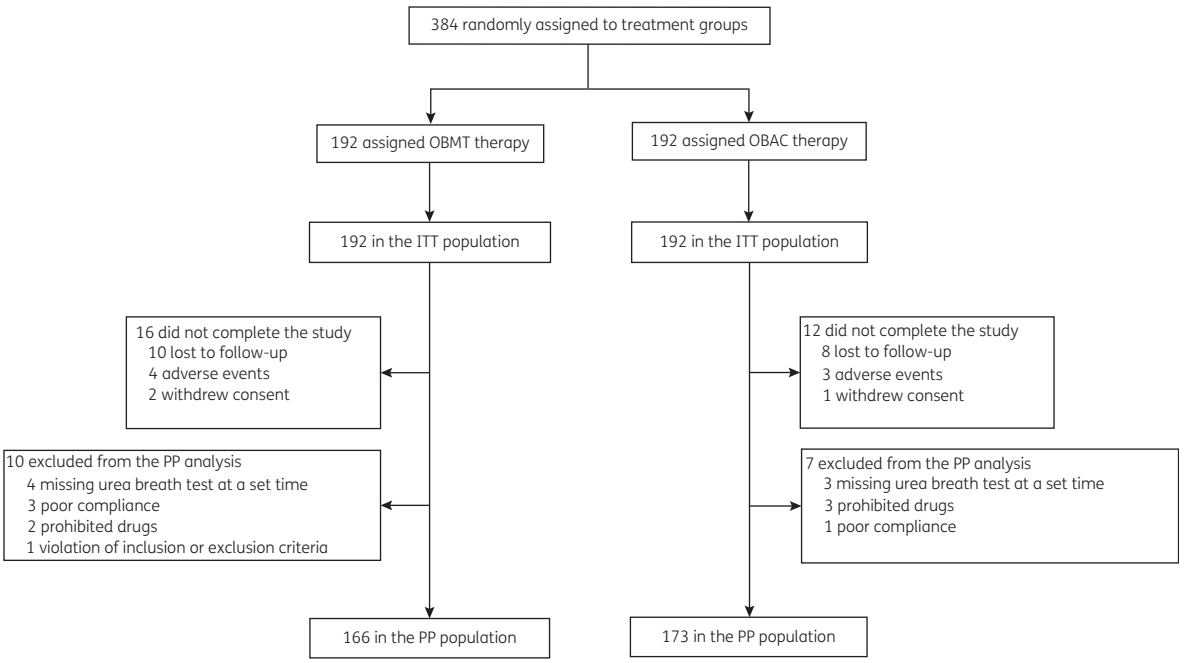

Figure 1. Trial flowchart. UBT, urea broth test.

assigned to receive OBMT therapy and 192 patients were randomly assigned to receive OBAC therapy. Forty-five patients were excluded from the PP analysis (26 in the OBMT group and 19 in the OBAC group). Table 1 shows the baseline characteristic data for the two treatment groups.

Eradication rate of H. pylori

The overall eradication rates in the ITT and PP populations are summarized in Table 2. Eradication rates for the OBMT versus OBAC therapies in the ITT population were 86.46% versus 87.50% ($P = 0.762$) and the rates were 94.58% versus 93.06% in the PP population ($P = 0.563$). The above differences between OBMT and OBAC therapies were not statistically significant.

Eradication rate related to antibiotic resistance

Table 3 presents the eradication rates according to metronidazole resistance and clarithromycin resistance in the PP population. Because amoxicillin resistance and tetracycline resistance were so rare we did not include them in further analyses.

Metronidazole resistance was similar for the OBMT (82.2%) and OBAC (78.1%) groups ($P = 0.463$) and did not significantly affect the eradication rates for either OBMT or OBAC therapy (both $P > 0.05$). Meanwhile, there were no significant differences in the eradication rates between OBMT and OBAC therapies for both metronidazole susceptible and resistant groups (both $P > 0.05$).

Clarithromycin resistance was similar between the OBMT (37.6%) and OBAC (30.5%) groups ($P = 0.279$). In the OBMT group, the clarithromycin resistance did not significantly influence the efficacy ($P = 1.000$). In the OBAC group, although patients with clarithromycin-susceptibile isolates achieved a higher cure rate than those with clarithromycin-resistant isolates (97.26% cure rate for clarithromycin-susceptible versus 87.50% for clarithromycin-resistant), the differences failed to reach statistical significance ($P = 0.127$). In addition, significant differences in eradication rates in the two therapies were not found in either clarithromycin susceptible or clarithromycin resistant groups (both $P > 0.05$).

Similarly, dual clarithromycin and metronidazole resistance (33.7% of the OBMT group and 27.6% of the OBAC group, $P = 0.347$) seemed to affect the eradication rate in the OBAC group (97.37% cure rate for non-dual resistance strains versus 86.21% for dual resistant strains), but the differences failed to reach statistical significance ($P = 0.083$). In the OBMT group, the clarithromycin resistance

Table 1. Baseline characteristics of the study groups

	OBMT ($N = 192$)	OBAC ($N = 192$)	P
Gender, *n* (%)			0.144
male	109 (56.77)	124 (64.58)	
female	83 (43.23)	68 (35.42)	
Age (years)			0.751
mean ± SD	41.75±11.94	41.36±12.14	
median (minimum–maximum)	44 (18–65)	42 (19–66)	
BMI (kg/m^2)			
mean ± SD	22.73±3.15	22.68±3.09	0.904
median (minimum–maximum)	22.52 (14.36–33.14)	22.59 (15.92–34.97)	
Ethnicity, *n* (%)			0.724
Han	189 (98.44)	187 (97.40)	
other	3 (1.56)	5 (2.60)	
Culture, *n* (%)			1.000
H. pylori positive	117 (60.94)	118 (61.46)	
H. pylori negative	75 (39.06)	74 (38.54)	

did not significantly influence the efficacy ($P = 0.880$). In the dual resistance group, there was no significant difference of eradication rate between the two therapies (OBMT 94.12% versus OBAC 86.21%, $P = 0.525$), though there was a trend toward a lower eradication rate of about 8%. Meanwhile, significant difference of the two therapies was not found in the non-dual-resistance group ($P = 0.201$).

Compliance

The compliance rate was 95.31% (183/192) and 98.44% (189/192) for OBMT therapy and OBAC therapy, respectively ($P = 0.078$).

TEAEs

TEAEs were evaluated in all 375 patients who received at least one dose of study medications. The frequencies of TEAEs are summarized in Table 4. Adverse events were recorded in 76 of 186 (40.86%) patients in the OBMT group and 70 of 189 (37.04%) patients in the OBAC group. Gastrointestinal symptoms, including nausea, vomiting, diarrhoea and discoloured faeces, and the CNS symptom dysgeusia were the most commonly reported TEAEs. All TEAEs were graded as mild. However, nine patients discontinued the study because of adverse events; four patients in the OBMT group because of adverse events (dizziness, dysgeusia, rash and accidental pregnancy) and three in the OBAC group because of adverse events (rash, nausea and vomiting).

Discussion

Our multicentre, randomized trial indicates that OBMT therapy achieves *H. pylori* eradication rates of 94.58% by PP analysis and 86.46% by ITT analysis, which is as effective as the widely used OBAC therapy. More than 95% of patients were compliant with study medication in both therapy groups.

The OBMT therapy achieving desired eradication rates for *H. pylori* is in line with the available medical literature that used the similar three-in-one capsule with PPI in first-line treatment.[18–22] An international study, which assessed the efficacy of 10 days of OBMT therapy, reported *H. pylori* eradication rates >90%.[19]

Table 2. Eradication rates in the PP and ITT populations

Population	OBMT	OBAC	*P*
PP	157/166 (94.58%)	161/173 (93.06%)	0.563
ITT	166/192 (86.46%)	168/192 (87.50%)	0.762

Table 4. TEAEs in the study groups

	OBMT ($N = 186$)	OBAC ($N = 189$)
TEAEs, *n*	76	70
Gastrointestinal disorders, *n* (%)		
diarrhoea	6 (3.23)	4 (2.12)
nausea	14 (7.53)	8 (4.23)
vomiting	8 (4.30)	4 (2.12)
faeces discoloured	8 (4.30)	7 (3.70)
flatulence	2 (1.08)	4 (2.12)
abdominal pain	4 (2.15)	4 (2.12)
constipation	2 (1.08)	2 (1.06)
CNS disorders, *n* (%)		
dysgeusia	7 (3.76)	15 (7.94)
dizziness	5 (2.69)	3 (1.59)
somnolence	4 (2.15)	2 (1.06)
Infections and infestations, *n* (%)		
upper respiratory tract infection	3 (1.61)	2 (1.06)
influenza	4 (2.15)	2 (1.06)
pyrexia	1 (0.54)	2 (1.06)
Musculoskeletal disorders, *n* (%)		
back pain	1 (0.54)	0
leg pain	0	2 (1.06)
arthralgia	2 (1.08)	0
Skin disorders, *n* (%)		
rash	4 (2.15)	7 (3.70)
pruritus vulvae	1 (0.54)	0
Psychiatric disorders, *n* (%)		
insomnia	0	2 (1.06)

Table 3. Eradication rates and antibiotic resistance in the PP population

	OBMT ($N = 101$)		OBAC ($N = 105$)	
Eradication rate by baseline metronidazole resistance				
baseline metronidazole resistance	yes	no	yes	no
eradication	76/83 (91.57%)	17/18 (94.44%)	76/82 (92.68%)	23/23 (100%)
P	1.000		0.408	
Eradication rate by baseline clarithromycin resistance				
baseline clarithromycin resistance	yes	no	yes	no
eradication	35/38 (92.11%)	58/63 (92.06%)	28/32 (87.50%)	71/73 (97.26%)
P	1.000		0.127	
Eradication rate by baseline combined metronidazole and clarithromycin resistance				
baseline dual metronidazole and clarithromycin resistance	yes	no	yes	no
eradication	32/34 (94.12%)	61/67 (91.04%)	25/29 (86.21%)	74/76 (97.37%)
P	0.880		0.083	

Another two prospective studies confirmed the desired eradication rates for *H. pylori* treatment, by using a three-in-one capsule plus PPI.[21,22] Moreover, the finding was corroborated by two recent randomized, open-label, Phase 3 trials, one conducted in the USA[18] and one conducted in Europe,[20] which showed that the three-in-one capsule was significantly better than standard triple therapy in the eradication of *H. pylori*. In addition, the same effectiveness has been recently found with respect to rescue therapy in patents failing eradication.[23,24]

Eradication rates of *H. pylori* have been decreasing to below 80% recently with the use of clarithromycin-based triple therapy worldwide.[10,25] Bismuth salts, topical agents that are available in our country, co-administrated with antibiotics against *H. pylori* can hinder the emergence of antibiotic resistance, inhibit the growth of *H. pylori* and improve the efficacy of eradication treatment.[26–31] In agreement with recent reports, OBAC therapy achieves desired eradication rates in our study.[11,32,33] Furthermore, bismuth-containing quadruple therapy is the recommended treatment in China and many other countries.[14–16]

Antibiotic resistance is an important factor for the failure of *H. pylori* eradication, particularly in China. *H. pylori* strains in China have demonstrated high resistance to metronidazole and clarithromycin, whereas the resistance to amoxicillin, tetracycline and furazolidone was quite low.[7,16] The rates of resistance to metronidazole and clarithromycin were 71.5% and 30.2% in this study, respectively. In addition, resistance to both metronidazole and clarithromycin was seen in 27.2% of isolates.

Metronidazole resistance was common (71.5%) in this study, which is similar to other data on resistance from the China.[7,16] In OBMT therapy, resistance to metronidazole has only a slight effect on the efficacy (94.44% cure rate for metronidazole-susceptible strains versus 91.57% for metronidazole-resistant strains). Therefore, the results indicate that the OBMT therapy appeared to overcome *H. pylori* resistance to metronidazole and was confirmed by two recent randomized, open-label, Phase 3 trials, conducted in the USA and Europe,[18,20] using the similar three-in-one capsule plus omeprazole.

The Maastricht V/Florence Consensus Report on *H. pylori* management claims that in regions of high dual clarithromycin and metronidazole resistance, bismuth-containing quadruple therapies are the treatment of choice for first-line empirical treatment. Ideally, clarithromycin should be avoided and a combination of alternative antibiotics for which resistance does not become problematic (e.g. amoxicillin, tetracycline, furazolidone, rifabutin) should be used.[4] Clarithromycin resistance was over 30% in both therapy groups of our study. No strategy has been shown to help in overcoming clarithromycin resistance and clarithromycin adds very little to treatment regimens in strains with *in vitro* clarithromycin resistance. In the OBAC group, although the clarithromycin resistance did not affect the efficacy significantly, there was a trend toward a lower eradication rate (97.26% cure rate for clarithromycin-susceptible strains versus 84.45% for clarithromycin-resistant strains). However, the eradication rate was acceptable and not influenced by clarithromycin resistance in the OBMT group. The same results were found in the dual clarithromycin and metronidazole resistance group patients. The high eradication rates obtained with OBMT therapy are not surprising, because the regimen does not contain clarithromycin and there is rare cross-resistance with metronidazole or with tetracycline. Therefore, non-clarithromycin bismuth-containing quadruple treatments should be recommended in regions of high clarithromycin resistance.

In order to improve patient convenience and reduce multiple drug combinations, the high-dose dual PPI/amoxicillin therapy should also be mentioned, which has been reported to have >90% cure rates in some studies, but the results varied in different countries.[34–38] In China, one study was performed to compare the efficacy of two optimized high-dose dual therapies with a bismuth-containing quadruple regimen for treating *H. pylori* infection and the results failed to show the acceptable eradication rate in the patients with high-dose dual therapy and held no advantage over the bismuth-containing quadruple therapy.[39] Therefore, further studies are still needed to explore the feasibility of dual therapy against *H. pylori*, especially in China.

Our study showed that the treatment was well tolerated, as more than 95% of patients were compliant with study medication in both the OBMT group and the OBAC group. The percentage of TEAEs in the OBMT group was 40.9%, which was lower than that reported in an American trial (58.5% of patients) and in a European trial (47.0% of subjects).[18,20] Moreover, no severe TEAEs or deaths occurred in the study. Therefore, the compliance and safety of the OBMT therapy was well accepted.

There are several limitations of this study. First, the *H. pylori* culture was positive in about 60% of the cases, which is low compared with the reported study.[20] Second, there was no long-term follow-up on the impact on gut microbiota, which is the research focus at present. Third, our study ended 3 years ago, which renders the results somewhat outdated.

In conclusion, the *H. pylori* eradication rate of 10 day single-capsule OBMT quadruple therapy is effective in China, regardless of metronidazole and clarithromycin resistance, and safe in clinical practice. Thus, this OBMT quadruple therapy consisting of the single (three-in-one) capsule and omeprazole can be recommended for first-line empirical treatment of *H. pylori* infection in China, especially the high clarithromycin and/or metronidazole resistance areas.

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Transparency declarations

None to declare.

Author contributions

Y. X. and X. P.: acquisition of data, analysis and interpretation of data, statistical analysis and drafting of the manuscript. Y. L., H. W., Y. D., J. X., J. W.,

Z. Z., Y. C., G. Z., K. W. and D. L.: acquisition of data and administrative, technical or material support. N. L. and Y. X.: study concept and design, revision of the manuscript for important intellectual content and study supervision. All authors approved the final version of the manuscript.

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