Original Article

Optimized high-dose amoxicillin–proton-pump inhibitor dual therapies fail to achieve high cure rates in China

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Abstract

Background\Aim: Quadruple daily administration of proton-pump inhibitor (PPI) therapy achieves potent acid inhibition, and combined with amoxicillin, with its pharmacodynamic and pharmacokinetic characteristics, may be efficient for *Helicobacter pylori* eradication. We compared the efficacy of two optimized high-dose dual therapies with a bismuth-containing quadruple regimen for treating *H. pylori* infection. Rabeprazole dosages for *H. pylori* eradication were also evaluated.

Patients and Methods: Treatment-naive and *H. pylori*-positive subjects were recruited and randomly apportioned to three treatment groups: Group A (n = 87), rabeprazole 10 mg plus amoxicillin 750 mg (4 times/day for 14 days); Group B (n = 87), rabeprazole 20 mg plus amoxicillin 750 mg (4 times/day for 14 days); and Group C (n = 89), bismuth-containing quadruple regimen consisting of rabeprazole 20 mg, bismuth 220 mg, amoxicillin 1000 mg, and clarithromycin 500 mg (2 times/day for 14 days). Four weeks after treatment discontinuation, patients were examined for *H. pylori* infection by ^{13}C-urea breath test. The rates of adverse effects, compliance, and eradication were evaluated.

Results: Eradication rates in groups A, B, and C were 78.1, 81.6, and 84.3%, respectively, based on intention-to-treat analysis, or 79.1, 83.5, and 86.2%, according to per-protocol analysis. Rates of adverse events and compliance of the three groups were similar.

Conclusion: For treating *H. pylori* infection, optimized high-dose amoxicillin–PPI dual therapies failed to achieve high cure rates in China and held no advantage over a bismuth-containing quadruple regimen.

Keywords: Amoxicillin, bismuth-containing quadruple regimen, dual therapy, eradication rate, *Helicobacter pylori*

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative, microaerophilic, and spiral-shaped pathogenic bacterium that was initially described in chronic gastritis patients by Marshall and Warren in 1983.[1] The multiplication of *H. pylori* in gastric mucosa causes inflammation and gastric mucosal damage that result in gastrointestinal diseases, and even extra-gastrointestinal diseases such as iron deficiency anemia, urticaria, and some cardiovascular diseases.[1-4] Multicenter studies in China showed that resistance rates of *H. pylori* to metronidazole, clarithromycin, and amoxicillin were 75.65, 27.6, and 2.7%, respectively, and the dual resistance rate

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to metronidazole and clarithromycin was 42.1%.[5,6] Thus, the eradication rates of traditional triple therapy have decreased significantly in most regions, even to the unacceptable level of <80%.[7] Other alternative therapies, such as sequential and combination therapies, are designed to raise eradication rates by increasing the number of antibiotic types (three or four), but the effects are not clear, and these are accompanied by many adverse reactions. The increased use of antibiotics also reduces rescue therapy options when first-line treatment fails.[8]

Proton-pump inhibitors (PPIs), a group of drugs that reduce gastric acid, may increase the activity and stability of antibiotics by elevating gastric pH and influencing the growth of *H. pylori*. Thus the degree and duration of acid suppression are linked to the cure rate. Studies regarding the association between intragastric acidity and the success of *H. pylori* eradication indicated that a pH > 4 should be sustained for throughout 24 h and 24 h-pH > 6.0.[9-11] However, standard PPI therapy (qd or bid) often fails to maintain a long-term increase in intragastric pH > 4.0.[12,13] Increasing the eradication rate requires more frequent and higher doses of PPIs. Research by Sugimoto *et al.*[9-11] suggest that quadruple daily administration of PPI therapy inhibits acid secretion within 24 h, irrespective of CYP2C19 (cytochrome P450 family 2 subfamily C member 19) genotype.[9,14] Further, amoxicillin, a β-lactam antibiotic, has been widely used in the eradication of *H. pylori*, and the rates of primary or acquired resistance are low.[15-17] The antibiotic effects of amoxicillin are time- and pH-dependent.[18,19] Four times daily administration can exert maximum bactericidal action, which is in accord with the fact that time is the most important pharmacodynamic parameter in β-lactam antibiotic dosage.[20]

In a setting of high drug resistance, bismuth-containing quadruple therapy has attracted widespread attention for first-line or rescue treatment in China. However, there are also many limitations, such as multiple drug combinations, complicated protocol, high cost, adverse side effects, and poor patient compliance.[8,21] Recently, Yang *et al.*[22] reported that a high-dose dual therapy consisting of amoxicillin and rabeprazole achieved an eradication rate of 95.3% in first-line therapy, and 89.3% in rescue therapy. This observation provides a new strategy for *H. pylori* treatment in China and other developing countries, where antibiotic resistance against *H. pylori* is high. Thus, we conducted this study to evaluate the efficacy of a dual therapy consisting of rabeprazole and amoxicillin to treat *H. pylori* infection, relative to that of a bismuth-containing quadruple regimen. We also explored the reasonable dosage for a PPI, for the purpose of determining an optimized therapeutic regimen for *H. pylori* treatment in China.

PATIENTS AND METHODS

Study participants

This randomized, open-label pilot study was conducted in local hospitals. The Research Ethics Committee of the local university approved the study, and registered it as ChiCTR-IOR-15007306.

Patients who received a diagnosis of chronic gastritis and uncomplicated peptic ulcer by endoscopy were recruited (n = 263 subjects, aged 18–70 years). All subjects provided written informed consent.

Patients with the following were excluded: treatment history of *H. pylori* infection; previous gastric surgery; gastric mucosa with high-grade intraepithelial neoplasia; pregnant or lactating; alcoholism; some major systemic diseases; severe complications of peptic ulcer disease; allergy to any medication in the regimens of the study; participation in other drug studies in the previous 3 months; unable to complete the follow-up; or incompliance. In addition, patients taking antibiotics, bismuth, probiotics, H2 blockers, PPIs, nonsteroidal antiinflammatory drugs, or adrenal corticosteroids in the preceding 4 weeks were excluded from this study.

Study protocols

Infection by *H. pylori* in the 263 patients was determined via carbon-13 (^{13}C) urea breath test, or rapid urease test, or *H. pylori* culture in solid selective, enriched medium. Each patient was randomly assigned to 1 of 3 treatment groups (R10A, R20A, or RBAC) based on a randomized digital table designed by Excel. Group R10A (n = 87), group R20A (n = 87), or group RBAC (n = 89) received 10 mg or 20 mg of rabeprazole plus 750 mg amoxicillin (R10A or R20A, respectively, each 4 times/day for 14 days), or a bismuth-containing quadruple regimen of 20 mg rabeprazole, 220 mg bismuth, 1000 mg amoxicillin, and 500 mg clarithromycin (RBAC; 2 times/day for 14 days) [Figure 1]. Drugs in dual-therapy regimens were taken before and after each meal, and the last time before going to bed. Drugs in the quadruple regimen were taken before and after breakfast and dinner.

Rabeprazole sodium enteric-coated capsules were purchased from Zhuhai Rundu Pharmaceutical, China. Amoxicillin was supplied by United Laboratories, China. The bismuth potassium citrate oral solution was made up in Daping Hospital. The clarithromycin tablets were purchased from Shanghai Abbott Laboratories, China.

All patients were informed regarding the drug administration schedule and possible adverse effects such as taste disorder, or black discoloration of stool during bismuth use. Patients were also cautioned to avoid acidic foods, alcohol, and tobacco. They were also warned of the possibility of serious unbearable side effects that could cause termination of therapy, and the way to report an adverse reaction. Patients were given written instructions regarding use of the medications. PPI and bismuth were administrated half an hour before meals and antibiotics after meals.

A follow-up phone call was performed after the first and tenth day of treatment. Four weeks after the completion of therapy, each patient was examined for *H. pylori* eradication by 13C-UBT.

Sample size estimation and statistical analysis

The sample size for multiple sample rates was calculated based on the assumption that the eradication rates would be 76 and 95.3% in the high-dose dual therapy and bismuth-containing quadruple regimens, respectively.[22,23] Thus, we estimated that 263 subjects were required for this study of three groups, with a power of 90% at a 5% statistically significant level, and assuming a ~20% dropout rate.

Statistical Package for the Social Sciences Statistics for Windows version 17.0 was used for data analysis. A P value <0.05 was regarded as statistically significant. The eradication rates and 95% confidence interval (CI) were calculated via intention-to-treat and per-protocol analyses. The Chi-squared test was used to assess variance in the eradication rates and side effects. Potential associations between the therapy regimens and characteristics of patients were analyzed by χ^2 test. These characteristics included: gender; lifestyle; educational level; endoscopic diagnosis; family member information (such as living region and number of family members); and compliance. One-way analysis of variance was used to investigate associations between the respective therapies and age or body mass index.

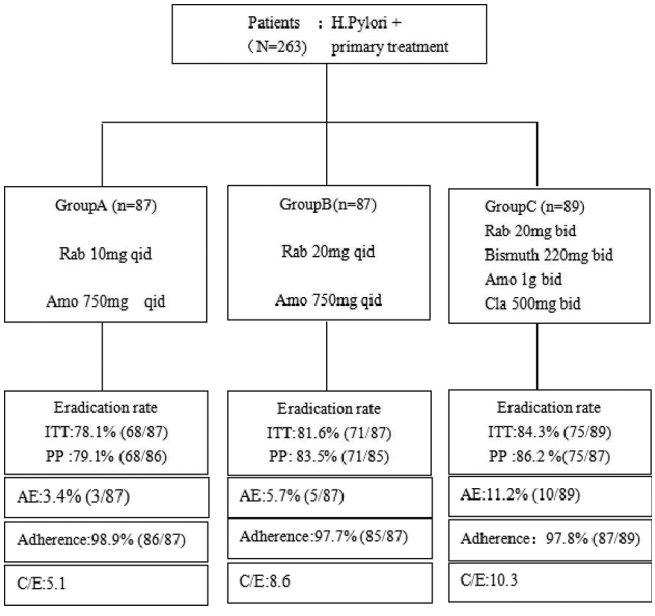

Figure 1: Flowchart of this study with eradication rate, AE, and adherence. *ITT: intention-to-treat; PP: per-protocol; AE: adverse events

RESULTS

A total of 263 eligible subjects were recruited for this trial [Table 1]. Patient compliance was defined as the completion of at least 80% of the drugs. Five patients were excluded due to withdrawal of consent, loss to follow-up, or poor adherence (1, 2, and 3 from groups R10A, R20A, and RBAC, respectively). The three groups were comparable with regard to gender, age, body mass index, number of family members, lifestyle habits, and clinical data.

Regarding rates of eradication of *H. pylori*, the intention-to-treat analysis showed no significant difference among the groups (P = 0.580) [Table 2]. Based on a per-protocol analysis, there was no significant difference

Table 1: Demographics and clinical data of patients in the R10A, R20A, and RBAC groups*

	R10A	R20A	RBAC	*P*
Patient, *n*	87	87	89	-
Male, *n*	34.4 (30/87)	39.0 (34/87)	44.9 (40/89)	0.363
Age, years	46.3±9.4	46.1±12.2	46.0±11.2	0.991
Body mass index, kg/m^2	22.1±2.7	22.7±3.1	22.7±2.8	0.302
Living in city	73.5 (64/87)	75.9 (66/87)	75.3 (67/89)	0.936
Family members	3.6	3.9	3.6	0.149
Education >high school	40.2 (35/87)	50.6 (44/87)	30.1 (33/89)	0.168
Smoking	17.2 (15/87)	12.6 (11/87)	23.6 (21/89)	0.163
Regular alcohol use	17.2 (15/87)	19.5 (17/87)	20.2 (18/89)	0.870
Peptic ulcer disease	12.6 (11/87)	6.9 (6/87)	14.6 (13/89)	0.226

*Demographics and clinical data of patients from three groups are presented as mean ± standard deviation or % (*n*/*N*), unless noted otherwise. None of the characteristics, including gender, age, body mass index, lifestyle habits, educational level, and clinical data showed any statistically significant differences among the groups

Table 2: *H. pylori* eradication rates in the R10A, R20A, and RBAC groups by intention-to-treat and per-protocol analyses*

	R10A	R20A	RBAC	*P*
Intention-to-treat				
Eradication rate	78.1% (68/87)	81.6% (71/87)	84.3% (75/89)	0.580
95% CI	68.4-86.8	73.5-89.7	76.7-91.9	
Per-protocol				
Eradication rate	79.1% (68/86)	83.5% (71/85)	86.2% (75/87)	0.452
95% CI	70.5-87.7	75.6-91.4	78.9-93.5	

*Eradication rates of three groups were tested by intention-to-treat and per-protocol analyses. No statistically significant differences were observed among the groups

in eradication rates ($P = 0.452$). Notably, by both methods of analysis, eradication was <85% in the R10A or R20A groups. Eradication was >85% only in the RBAC group (86.2%, 95% CI 75.6–91.4), according to the per-protocol analysis. These data indicated that the efficacy of the three regimes was very similar.

The occurrence of side effects such as parageusia and black teeth and black tongue tended to be higher in group RBAC than in groups R10A or R20A, although the difference was not significant [Table 3].

DISCUSSION

H. pylori infection was first identified as an infectious disease in the Kyoto global consensus report.[24] It leads to chronic active gastritis, peptic ulcers, and gastric cancer. As in asymptomatic syphilis or tuberculosis, the rate of progression in asymptomatic *H. pylori* gastritis without complications is unpredictable. Eradication of *H. pylori* would reduce the reservoir of infected individuals, and avoid the associated costs of diagnosis and treatment of this and its related diseases.[24] This pilot study evaluated the effects of two dual-therapy regimens (rabeprazole and amoxicillin) for active *H. pylori* infections relative to that of a bismuth-containing quadruple regimen (RBAC).

A dual therapy consisting of a PPI and amoxicillin twice daily was first introduced in the 1990s as a first-line regimen against *H. pylori* infection. As the eradication rate was not satisfactory, it was subsequently used as a salvage treatment;[24] the eradication rate of salvage therapy consisting of rabeprazole (10 mg 4 times/day) and amoxicillin (500 mg 4 times/day) could reach 90%.[25] The above observation was in agreement with the study of Yang *et al.*,[22] who showed high eradication rates of *H. pylori* after high-dose dual therapies (rabeprazole 20 mg and amoxicillin 750 mg 4 times/day) in a multicenter randomized controlled trial. These results indicated that the key to a successful dual-therapy regimen is a PPI-generated neutral environment suitable for bacterial growth and entry into a replicative state of the dormant *H. pylori* residue, which makes *H. pylori* sensitive to amoxicillin. Amoxicillin administrated four times daily could maximize its antibiotic effects. Like other microorganisms, *H. pylori* could exist as persister cells after the therapy was completed. This nonreplicating state is described as phenotypic resistance, which requires an acidic environment.[26,27] An increase in the dosage of rabeprazole can overcome the influence of a CYP2C19 gene polymorphism on gastric pH, suppress acid secretion, and provide a neural environment to transform the dormant *H. pylori* residue into a replicative state and susceptible to antibiotics.

Our data showed that, according to the intention-to-treat analysis, a 14-day protocol with rabeprazole, 10 or 20 mg (R10A and R20A), and amoxicillin 750 mg four times daily achieved an *H. pylori* eradication rate of 78.1 or 81.6%, respectively, while the eradication rate of the bismuth-containing quadruple regimen (RBAC) was 84.3%. Compared with the RBAC group, the R10A and R20A groups were similar in terms of *H. pylori* treatment effects, and showed a lower eradication rate than the study of Yang *et al.*[22] In the report by Yang *et al.*,[22] patients with extensive, intermediate, or poor metabolizers of the CYP2C19 gene accounted for 43.6, 43.6, and 12.8%, respectively, of the study population. In our previous studies from Chongqing, China,[22,28] these accounted for 44.4, 45.8, and 9.8% of the patients. The prevalence of amoxicillin resistance was 0–3.6% and 0% in Taiwan and Chongqing, respectively. In these two studies,[22,28] there were no differences in CYP2C19 gene polymorphism and the prevalence of amoxicillin resistance among the subjects.

In the present intention-to-treat analysis, the clarithromycin-containing bismuth quadruple therapy

Table 3: Adverse events and protocol adherence in the R10A, R20A, and RBAC Groups[a]

Parameter	AE, *n*	R10A	R20A	RBAC	*P*
Patients with AE		3.4% (3/87)	5.7% (5/87)	11.2% (10/89)	0.109
	Total	5	5	16	
	Pruritus	2	0	0	
	Rash	2	0	0	
	Palpitation	1	1	0	
	Diarrhea	0	2	0	
	Abdominal pain	0	0	1	
	Nausea	0	0	1	
	Dizziness	0	1	0	
	Parageusia	0	1	8	
	Teeth blackened	0	0	6	
Adherence[b]		98.9% (86/87)	97.7% (85/87)	97.8% (87/89)	0.821

Adverse events and protocol adherence were not statistically significant among the three groups. [a]Data are presented as % (*n*/*N*) unless noted otherwise; [b]Protocol adherence defined as completion of ≥80% of drugs. AE, adverse events

delivered an 85% eradication rate. Another trial of bismuth quadruple therapy containing clarithromycin achieved better curative rates of eradication (88.8 and 94.9% based on intention-to-treat and per-protocol analyses, respectively).[29] Resistance to clarithromycin influenced treatment efficacy: eradication rates of the clarithromycin-containing bismuth quadruple therapy with the clarithromycin susceptible strains were 98.6%, and 76.9% with resistant strains ($P = 0.001$).[29] Sensitivity to clarithromycin may be a key factor in our research influencing the eradication regimen curative effect, but unfortunately a test of susceptibility to clarithromycin was not conducted.

There are three main potential reasons that the results of the dual therapy of the present study were not as outstanding as previous reports. First, there was no information regarding intragastric pH values. A pH > 6 is essential to the success of dual therapy on *H. pylori* eradication. Due to experimental limitations, we were not able to test the patients' intragastric pH consistently.

Secondly, the effects of amoxicillin during dual therapy on morphological changes of *H. pylori* may be unrecognized.[30,31] Studies have shown that amoxicillin at minimal inhibitory concentrations promotes the transformation of *H. pylori* from a spiral to a coccoid form that is resistant to amoxicillin; the coccoid form contributes to treatment failures and relapses of infection in patients with lower metabolic status. A therapy protocol that can eradicate both spiral and coccoid forms of *H. pylori* and prevent the occurrence of coccoid forms is needed. In our study, amoxicillin 750 mg four times daily was applied to maintain a minimal inhibitory concentration. However, the morphology of *H. pylori* was not investigated.

Thirdly, *H. pylori* virulence factors may be involved in the different types of *H. pylori*-associated diseases and their effects on *H. pylori* eradication.[32] In Yang *et al.*'s[22] study, patients with peptic ulcer accounted for 65% of the total, but only 10% in ours. It is believed that the cure rate for *H. pylori* infection in peptic ulcer patients is relatively higher than that of patients with other types of *H. pylori*-related conditions. Formulating treatment protocols based on virulence factors and local antibiotic susceptibility tests may help enhance the efficacy rate of therapy.

The eradication rate of the RBAC regimen (14-day bismuth-containing quadruple therapy) in our study was only 84.3%. Other studies in China showed that furazolidone or tetracycline bismuth-containing quadruple therapy could achieve a ≥90% eradication rate.[33,34] This discrepancy is possibly due to resistance to clarithromycin. It may be that furazolidone or tetracycline should be used in bismuth-containing quadruple therapy.

In the present study, the eradication rate of group R10A (10 mg rabeprazole plus 750 mg amoxicillin) was lower than 80%. Thus, it was not considered suitable for empirical therapy. Rather, the bismuth-containing quadruple therapy (RBAC) is still considered the first-line treatment, based on its eradication rate. However, a greater percentage of patients who received RBAC showed side effects such as parageusia, black teeth, and black tongue compared with the R10A or R20A groups. This was due to the bismuth and clarithromycin in the RBAC regimen. Nevertheless, the rate of incidence of adverse side effects and protocol compliance of the patients of the three groups were similar.

Due to experimental conditions and feasibility in clinical practice, we failed to monitor the gastric pH value and morphological changes of *H. pylori* in the patients' stomachs during the treatment, which may have contributed to the undesirable effects. Failure to perform pretreatment tests for antibiotic susceptibility (especially for amoxicillin and clarithromycin) and CYP2C19 polymorphism also made us unable to select appropriate antibiotics and the right PPI dosage. These shortcomings will be investigated and solved through another study in our lab on *H. pylori* resistance to six antibiotics and the distribution of CYP2C19 polymorphisms in the Chongqing population in China.

As high-dose dual therapy achieved a high rate of eradication of *H. pylori* infection in Taiwan, in this study we evaluated its effects relative to that of a RBAC regimen in mainland China. However, we failed to observe the acceptable eradication rate in the patients with dual therapy. Further studies are still needed to explore the feasibility of dual therapy against *H. pylori*. Bismuth-containing quadruple therapy is still recommended as the first-line regimen in clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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