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ORIGINAL ARTICLE

Randomized trial comparing rabeprazole- versus lansoprazole-based *Helicobacter pylori* eradication regimens

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Abstract Different types of proton pump inhibitor (PPI)-based triple therapies could result in different *Helicobacter pylori* eradication rates. This study aimed to compare the efficacy and safety of rabeprazole- and lansoprazole-based triple therapies in primary treatment of *H. pylori* infection. From September 2005 to July 2008, 426 *H. pylori*-infected patients were randomly assigned to receive a 7-day eradication therapy with either rabeprazole 20 mg bid (RAC group, $n = 222$) or lansoprazole 30 mg bid (LAC group, $n = 228$) in combination with amoxicillin 1 g bid and clarithromycin 500 mg bid. The patients received follow-up esophagogastroduodenoscopy (EGD) and/or ^{13}C-urea breath test 12–16 weeks later to define *H. pylori* status. Their personal and medical history, compliance and side effects were obtained by using a standardized questionnaire. Intention-to-treat analysis revealed that the eradication rate was 87.84% in the RAC group and 85.96% in the LAC group ($p = 0.56$). All patients

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returned for assessment of compliance (100% in the LAC group vs. 99.50% in the RAC group; $p = 0.32$) and adverse events (7.20% in the RAC group vs. 5.70% in the LAC group, $p = 0.51$). Univariate analysis suggested that patients with nonsteroid anti-inflammatory agent (NSAID) use had lower eradication rates than those without (76.71% vs. 88.74%; $p = 0.006$). Our results showed that efficacy and safety were similar in rabeprazole- and lansoprazole-based primary therapies. The influence of NSAID usage on *H. pylori* eradication needs to be further investigated.

Introduction

Helicobacter pylori infection causes gastrointestinal tract diseases such as peptic ulcers, gastritis, mucosa-associated lymphoid tissue lymphoma, and gastric cancer [1]. *H. pylori* eradication was proven to cure or improve these diseases. The eradication rate was much improved after proton pump inhibitors (PPIs) were included in the regimens. The Maastricht consensus report recommended PPI—amoxicillin—clarithromycin or metronidazole as the first-line treatment for *H. pylori* [2]. In Taiwan, the most widely used regimen is a PPI plus amoxicillin and clarithromycin; the eradication rate reaches 75—95% [3—8]. Factors that influence eradication efficacy include bacteria strain, antibiotic resistance, and patients' compliance [9].

PPIs are rapidly absorbed, highly protein bound, and metabolized in the liver by the cytochrome (CYP) P450 system, especially CYP2C19 [10—12]. PPIs play an important role in *H. pylori* eradication. They can affect the treatment efficacy through two possible mechanisms. Firstly, PPIs have antibacterial activity. Secondly, they suppress gastric acid secretion, through which the availability and activity of antibiotics is increased [9]. A previous study has suggested that increasing the PPI dose could improve the eradication rate [13]. However, different types of PPIs may have variable effects on gastric acid suppression and antibacterial activity. Their side effects, such as allergic reaction, dizziness, and gastrointestinal upset, may also influence patient compliance. Rabeprazole has the highest p*K*a and fastest onset of action [14,15]. It is metabolized through a nonenzymatic pathway and is less susceptible to the influence of genetic polymorphisms of CYP2C19. Therefore, patients on rabeprazole have similar pharmacokinetics and less drug interactions even if they have different hepatic metabolism rates [14]. Lansoprazole was marketed earlier than rabeprazole and has been proven to have good eradication rates and little side effects in clinical studies [9,16]. It is metabolized by CYP3A4 and CYP2C19. Clarithromycin significantly increases C_{max} of lansoprazole and, respectively, enhances the drug effect by inhibition of CYP3A4 [10,11,17]. Two Japanese studies have compared the efficacy and safety of rabeprazole- versus lansoprazole-based regimens in primary treatment of *H. pylori* infection [18,19]. However, results were not consistent. Moreover, the *H. pylori* resistance rates could be different in Taiwan compared with Japan, but no report regarding this has been seen in Taiwan.

Materials and methods

Patient selection

Potential cases were patients who visited the gastroenterological clinic of Kaohsiung Medical University Hospital between September 2005 and June 2008 with a complaint of epigastric discomfort. Esophagogastroduodenoscopy (EGD) was performed and those diagnosed of nonulcer dyspepsia (gastritis) or peptic ulcer with *H. pylori* infection were enrolled in this study. Peptic ulcer includes both duodenal and/or gastric ulcers. Exclusion criteria included: (1) ingestion of antibiotics, bismuth, or PPI within the prior 4 weeks; (2) patients with allergic history to the medications used; (3) patients with previous gastric surgery; (4) the coexistence of serious concomitant illness (e.g., decompensated liver cirrhosis, uremia); and (5) female patients who were pregnant.

Treatment regimen, randomization, and follow-up

The participants were randomly assigned to the RAC group (rabeprazole 20 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid for 7 days) or the LAC group (lansoprazole 30 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid for 7 days) according to the random number table. By starting from a certain row and column of the random number table, the serially enrolled patients obtained a number. Those with odd numbers were assigned to the RAC group and the opposite were assigned to the LAC group. Patients were asked to return during the 2nd week to assess drug compliance and adverse effects. The technicians who performed the *H. pylori* tests [culture, rapid urease test, and ^{13}C-urea breath test (UBT)] or filled in the questionnaires as well as the pathologists were blinded to the eradication regimens the patients received. All participants gave written informed consent. This study was approved by the Institutional Review Board of Kaohsiung Medical University.

Diagnosis of *H. pylori* infection

All participants underwent a UBT and EGD examination with biopsy of the gastric mucosa to establish *H. pylori* infection by rapid urease test, histology examination of *H. pylori* by haematoxylin and eosin stains and Giemsa stains, and *H. pylori* culture. The definition of *H. pylori* infection in this study required positive *H. pylori* culture or at least two

positives of UBT, rapid urease test, and histology examination. Patients were asked to receive EGD examinations with biopsy for rapid urease test, histology, and culture 12–16 weeks later to confirm *H. pylori* infection status. Failed *H. pylori* eradication was established if the culture was positive, or both rapid urease test and histology were positive. For patients who refused follow-up EGD, UBT was used to confirm *H. pylori* status.

Questionnaire

The questionnaire contained questions regarding personal history of smoking, alcohol drinking, regular usage of nonsteroid anti-inflammatory drug (NSAID), and presence of underlying systemic diseases. Smokers were those who consumed more than one pack of cigarettes a week and drinkers were those who drank more than one cup of alcoholic beverage a day. Regular NSAID users were defined as continuous consumption of NSAIDs for pain control for more than 1 month. In this study, they were also current users. Underlying systemic diseases included hypertension, diabetes mellitus, cerebral vascular accident, heart disease, chronic obstruction pulmonary disease, uremia, malignancy, viral hepatitis, and others. Compliance was defined as good (taken more than 70% of total medication) or poor by counting unused medication after treatment was completed. Adverse events included abdominal pain, diarrhea, constipation, dizziness, taste perversion, headache, anorexia, nausea, vomiting, skin rash, and others. Those who considered that those symptoms disturbed their daily life were defined to have positive adverse effects. Those who did not experience these symptoms or did experience them but did not consider them a disturbance to their daily life were defined as negative adverse effects.

Statistical analysis

The distribution of gender and the initial endoscopic diagnosis between patients in RAC and LAC groups were compared by Chi-square statistics. The same method was applied to compare the efficacy and the frequency of side effects of the two regimens. The analyzed efficacy outcome was cure of *H. pylori* infection. The difference of patients' ages in the two groups was examined using the Student *t* test. Subanalysis for aging, smoking, alcohol consumption, and NSAID use related to efficacy of *H. pylori* eradication was performed by Chi-square analysis. A two-sided p value < 0.05 was considered statistically significant. The data were analyzed using the SAS statistical package version 9.1 (SAS Institute, Cary, NC); all p values were two-sided. Assuming that the conventional eradication rate (LAC group) was 81%, and the RAC group achieved a 91% eradication rate (10% difference of increase) [19], our statistical power in this study would have 91% under the sample size of approximately 210 patients in each group and two-sided p value of 0.05 if 95% of patients completed the follow-up.

Results

In total, 24 of the 474 patients enrolled were excluded according to the exclusion criteria. A total of 426 of those interviewed using a standardized questionnaire received further *H. pylori* treatment. The 24 patients who refused to receive any follow-up examination for *H. pylori* infection were defined as treatment failure in intention-to-treat analysis (Fig. 1). In Table 1, we show the demographic characteristics of our study participants including the distribution of age, gender, personal history, underlying disease, and initial endoscopic diagnoses in RAC and LAC groups. Most were diagnosed with ulcer diseases (65.32% in the RAC group, 60.96% in the LAC group; $p = 0.34$). The prevalence of cigarette, alcohol, and NSAID consumption was similar in each group. The efficacy and safety profiles of the two regimens are shown in Table 2. In intention-to-treat analysis, 87.84% (195/222) and 85.96% (196/228) of patients in RAC and LAC groups, respectively, were free of *H. pylori* infection after eradication therapy ($p = 0.56$). In per protocol analysis, the *H. pylori* eradication rate was 91.98% in the RAC group and 91.59% in the LAC group ($p = 0.88$). There was no difference in eradication rate in the two groups. All study patients, except one in the RAC group, took at least 70% of prescribed medication; compliance was 99.5% in the RAC group and 100% in the LAC group. Among the 16 (7.2%) cases in the RAC group who reported adverse events, taste perversion (10 cases) and dizziness (5 cases) were the most common. A total of 13 (5.70%) patients in the LAC group reported adverse events and the most common complaints were taste perversion (6 cases) and dizziness (6 cases). There were no statistically significant differences in eradication rates, compliance rates, or the presence of adverse events.

Smoking and alcohol consumption did not significantly influence *H. pylori* eradication rates (Table 3). However, NSAID users were less likely to have successful *H. pylori* eradication than nonusers (76.71% vs. 88.74%; $p = 0.006$).

Discussion

Many studies have compared the effect of different PPI-based regimens on *H. pylori* eradication in many countries. A meta-analysis study in 2003 showed similar efficacy for *H. pylori* eradication when different PPIs were used [20]. A review article in China also revealed no difference in *H. pylori* eradication rate using different PPIs and the eradication rates reached around 80–90% in different studies [21]. Two studies compared the newer PPIs, rabeprazole versus lansoprazole. Miwa et al. reported similar eradication rates for RAC and LAC regimens (88.7% and 82.7%, respectively, 104 patients in both groups) [18]. However, Murakami et al. showed a significantly higher success rate with the RAC regimen (88%, 147 patients) than with the LAC regimen (78%, 148 patients) in intention-to-treat analysis [19]. Our previous study revealed that the *H. pylori* eradication rate reached 85–90% in intention-to-treat analysis and there was no significant difference in esomeprazole- and rabeprazole-based triple therapy [3]. This study also showed similar efficacy in lansoprazole- and rabeprazole-based triple therapy (85.96% and 87.84%; $p = 0.56$).

The common side effects of PPI-based therapy include abdominal discomforts (e.g., abdominal pain, diarrhea, constipation, and nausea), skin rash, taste perversion,

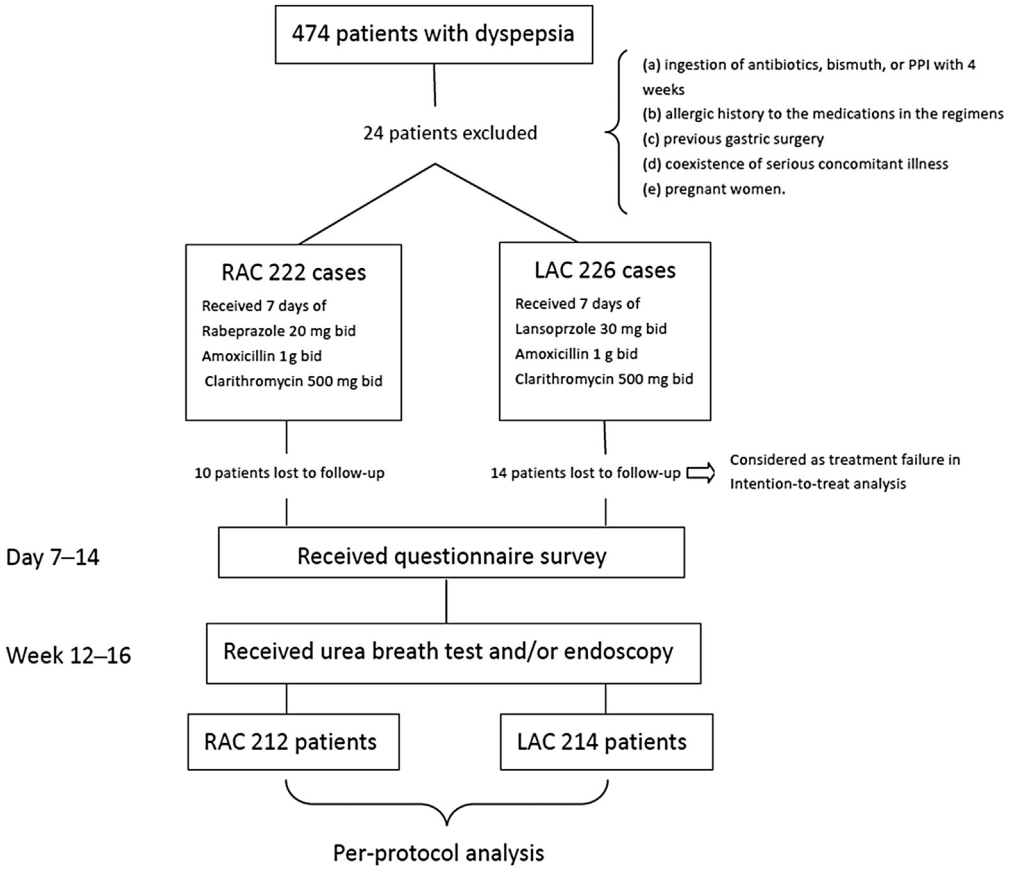

Figure 1. Consort diagram of the study design.

headache, and dizziness. In our study, the prevalence of adverse effects was around 6% in both groups. Taste perversion and dizziness were the most common among them. One study in Japan showed a higher frequency of adverse effects in patients receiving a higher dose of rabeprazole-based triple therapy (4.8% in 40 mg group vs. 0% in 20 mg group). However, compliance was similar in both groups [18]. The patients could tolerate both regimens well and showed good compliance.

Some personal habits, such as smoking and alcohol drinking, and some medications may cause drug interaction via hepatic metabolism, especially via the CYP 450 system. Previous studies including ours showed that smoking had little effect on eradication rates. However, Hsu et al. reported that alcohol consumption significantly lowered treatment efficacy (70% among drinkers vs. 90% among nondrinkers, $p = 0.004$) [6]. The possible mechanism stems from the stimulation of

Table 1 Demographic distribution of the participants receiving different eradication regimens.

	RAC group ($n = 222$)	LAC group ($n = 228$)	p
Age (y)			0.79
≤54	118 (53.15%)	124 (54.39%)	
>54	104 (46.85%)	104 (45.61%)	
Gender			
Male	94 (42.34%)	83 (36.4%)	0.19
Female	128 (57.66%)	145 (63.6%)	
Smoking[a]	32 (14.75%)	33 (14.47%)	0.94
Alcohol consumption[a]	13 (5.99%)	19 (8.33%)	0.33
NSAID use[b]	37 (16.89%)	36 (15.86%)	0.77
Diagnosis			
Gastritis	77 (34.68%)	89 (39.04%)	0.34
Peptic ulcer[c]	145 (65.32%)	139 (60.96%)	

LAC = lansoprazole, amoxicillin, and clarithromycin; RAC = rabeprazole, amoxicillin, and clarithromycin.
[a] Missing in five cases.
[b] Missing in four cases.
[c] Peptic ulcer = presence of gastric ulcer and/or duodenal ulcer.

Table 2 Outcomes of rabeprazole- and lansoprazole-based triple therapies.

	RAC group ($n = 222$)	LAC group ($n = 228$)	p
Eradication rate			
Intention-to-treat	87.84% (195/222)	85.96% (196/228)	0.56
Per protocol	91.98% (195/212)	91.59% (196/214)	0.88
Compliance	99.50% (221/222)	100% (228/228)	0.32
Adverse events	7.20% (16/222)	5.70% (13/202)	0.51

LAC = lansoprazole, amoxicillin, and clarithromycin; RAC = rabeprazole, amoxicillin, and clarithromycin.

Table 3 Univariate analysis of clinical factors influencing the efficacy of *H. pylori* eradication.

	Patients (*n*)	*H. pylori* eradication rate	*p*
Smoking[a]			0.58
(+)	65	84.61%	
(−)	380	87.10%	
Alcohol consumption[a]			0.34
(+)	32	84.38%	
(−)	413	86.92%	
NSAID use[b]			0.006
(+)	73	76.71%	
(−)	373	88.74%	

[a] Missing five cases.
[b] Missing four cases.

histamine release, gastric acid secretion [22,23], and a change of intragastric microenvironment that influences the stability of antibiotics or enhances the growth of *H. pylor*i [24]. However, such differences were not seen in our study (presence vs. absence of alcohol consumption: 84.38% vs. 86.92%, $p = 0.34$). A larger study with more detailed records of the amount and type of alcohol consumed is needed to clarify the association.

Aspirin and NSAIDs, commonly prescribed for antiatherosclerosis and pain control, often cause dyspepsia and have been reported to affect *H. pylori* treatment. Previous studies hypothesized that aspirin and NSAIDs could inhibit *H. pylori* growth *in vitro* and increase its susceptibility to antibiotics [25, 26]. A small Korean study compared the efficacy of the standard omeprazole—amoxicillin—clarithromycin (OAC) regimen (61 cases) with the OAC plus aspirin regimen (60 cases) and did not find a significant difference in eradication rates (per protocol analysis: 80.3% vs. 86.7%, $p = 0.472$) [25]. Recently, Zhang et al. [26] conducted a prospective case—control study in Turkey and reported a significantly higher eradication rate of triple therapy among aspirin users (Intention-to-treat analysis (ITT): 83% vs. 53%, $p < 0.05$). However, another retrospective observational study in Korea revealed a lower eradication efficacy for first-line treatment among aspirin users compared with nonusers (61.4% vs. 78.7%, $p = 0.001$) [27]. In that study, the eradication rate was similar among NSAID users and nonusers (70.8% vs. 77.2%, $p = 0.466$) [27]. Our crude result suggests that NSAID users have lower successful eradication than nonusers (76.71% vs. 88.74%, $p = 0.006$). The possible mechanism is that NSAIDs cause gastrointestinal damage and influence blood supply of gastric mucosa, which may decrease drug absorption and the bactericidal effect. The possible confounders were smoking, alcohol drinking, *H. pylori* strain (antibiotic resistance), drug interaction, and host susceptibility. However, we do not have information concerning the last three items. The distribution of smoking and alcohol, age and gender were similar in the two groups, and thus do not need to be further adjusted. All inconsistent findings may come from different study populations, bacteria strains, limited sample size, and study design. A larger randomized control study focusing on the effect of NSAIDs or aspirin on the treatment for *H. pylori* is needed to clarify the association.

The strengths of this study include: (1) this was a well-designed randomized trial with adequate study cases and considered some factors that may influence the results of *H. pylori* treatment; (2) the *H. pylori* status was confirmed by methods proven to have high accuracy to detect current infection; and (3) the compliance and adverse effects were carefully recorded soon after the patients finished the treatment course to avoid recall bias. However, we did not perform the *H. pylori* sensitivity test. Neither did we test the genetic polymorphisms concerning *CYP 2C19*, which might influence the metabolism of PPIs.

In conclusion, this study showed similar eradication rates for rabeprazole- and lansoprazole-based primary therapies for *H. pylori* infection. Both regimens were well tolerated and had good patient compliance. NSAIDs might decrease the efficacy of first-line therapy but this finding should be confirmed by a larger prospective study.

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