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BRIEF ARTICLE

Quadruple therapy for eradication of *Helicobacter pylori*

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Abstract

AIM: To investigate quadruple therapy with rabeprazole, amoxicillin, levofloxacin and furazolidone for the eradication of *Helicobacter pylori* (*H. pylori*) infection.

METHODS: A total of 147 patients were divided into the experimental treatment group (n = 78) and the standard triple treatment group (n = 69). The experimental treatment group received rabeprazole 20 mg, amoxicillin 1.0 g, levofloxacin 0.2 g and furazolidone 0.1 g, twice daily. The standard triple treatment group received omeprazole 20 mg, amoxicillin 1.0 g and clarithromycin 0.5 g, twice daily.

RESULTS: One month after treatment, the ^{13}C urea breath test was carried out to detect *H. pylori*. The eradication rate using per-protocol analysis was 94.3% in the experimental treatment group and 73% in the standard triple treatment group (P < 0.05), and using intention to test analysis, these figures were 86% and 67% in the two groups, respectively. Side effects were observed in 34 patients, and included mild dizziness, nausea, diarrhea and increased bowel movement. Eleven of the 34 patients needed no treatment for their side effects.

CONCLUSION: Rabeprazole, amoxicillin, levofloxacin and furazolidone quadruple therapy is a safe method for the eradication of *H. pylori* with high efficacy and good tolerability.

Key words: Rabeprazole; Amoxicillin; Levofloxacin; Furazolidone; *Helicobacter pylori*

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is closely related to a number of gastrointestinal diseases. It is the main pathogenic factor in chronic gastritis and peptic ulcer disease, and is also the initiating factor in gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma[1]. The ability to reliably eradicate this pathogen is important in the management of these diseases[2-5].

The eradication of *H. pylori* has been a research focus for the effective treatment of the above diseases. Currently, the worldwide standard triple therapy consists of a proton pump inhibitor (PPI) or bismuth, amoxicillin and metronidazole or clarithromycin. However, with the extensive use of antibiotics and the irregularity of treatment, there is increasingly high *H. pylori* resistance, especially resistance to metronidazole and clarithromycin. The effectiveness of "legacy triple therapy", which was recommended by the Maastricht Ⅲ Consensus Report, has demonstrated disappointingly low treatment success (*i.e.*, below 80%) worldwide[6]. The difficulty of *H. pylori* eradication is increasing. The consensus of the Third National Lushan Conference held at Lushan Mountain in Jiangxi in August 2007 states that there is high *H. pylori* resistance to metronidazole and clarithromycin, but low resistance to furazolidone, tetracycline and quinolones,

therefore, the effects of these antibiotics are relatively high, and may be used as the initial treatment choice. In our study, quadruple therapy with rabeprazole, amoxicillin, levofloxacin and furazolidone achieved good results.

MATERIALS AND METHODS

General information

All 147 patients underwent the treatment with either rabeprazole 20 mg, amoxicillin 1.0 g, levofloxacin 0.2 g and furazolidone 0.1 g, twice daily or omeprazole 20 mg, amoxicillin 1.0 g and clarithromycin 0.5 g, twice daily at the First Affiliated Hospital of Henan University of Science and Technology from January 2009 to December 2011 and were included in this study as sample cases. However, 78 patients who chose treatment with rabeprazole 20 mg, amoxicillin 1.0 g, levofloxacin 0.2 g and furazolidone 0.1 g, twice daily were included in the experimental treatment group, and 69 patients who chose treatment with omeprazole 20 mg, amoxicillin 1.0 g and clarithromycin 0.5 g, twice daily were included in the standard triple treatment group. All patients, who did not receive treatment before enrolling in this study, were diagnosed with chronic erosive gastritis or peptic ulcer disease by endoscopy. In addition, all patients had a positive rapid urease test and antrum mucosal tissue was obtained to detect the presence of *H. pylori*.

The patients by their own volition, were divided into the experimental treatment group (n = 78) and the standard triple treatment group (n = 69). The experimental treatment group consisted of 41 males and 37 females, aged 20 to 65 years, with an average age of 44.5 years; 34 patients had chronic erosive gastritis, 28 had a gastric ulcer and 16 had a duodenal ulcer. The standard triple treatment group consisted of 38 males and 31 females, aged 22 to 67 years, with an average age of 43.5 years; 31 patients had chronic erosive gastritis, 17 had a gastric ulcer and 21 had a duodenal ulcer. There were no statistically significant differences between the two groups regarding age and gender (Table 1).

Exclusion criteria

Patients with a history of gastrointestinal surgery, gastroesophageal reflux disease, non-steroidal anti-inflammatory drug-related stomach problems or ulcers, those taking PPIs or H_2 blockers, bismuth, antibiotics or other drugs which might affect gastric physiology two weeks before enrolling in the study and those who were allergic to the medicine tested were excluded.

Methods

The experimental treatment group received rabeprazole (Jiangsu Stockhausen Pharmaceuticals, Nanjing, China) 20 mg, amoxicillin (Shiyao Pharmaceutical Group, Shijiazhuang, China) 1.0 g, levofloxacin (Jiangsu Yabang Epson Pharmaceutical, Nanjng, China) 0.2 g and furazolidone (Wuhan Huawei Medicine, Wuhan, China) 0.1 g; the standard triple treatment group received omeprazole (Beijing Taiyang Pharmaceutical, Beijing, China) 20 mg, amoxicillin (Shiyao Pharmaceutical Group, Shijiazhuang, China) 1.0 g and clarithromycin (Guangzhou Baiyunshan Pharmaceutical Group, Guangzhou, China) 0.5 g. The drugs were given half an hour before meals in the morning and evening for 7 d.

Table 1 Baseline characteristics of the patients

Group	No. of patients	Age (yr)	Male[1]	Female[1]	Chronic erosive gastritis[2]	Gastric ulcer[2]	Duodenal ulcer[2]
Experimental treatment	78	44.5	41	37	34	28	16
Standard treatment	69	43.5	38	31	31	17	21

[1]χ^2 = 0.093, P > 0.05; [2]χ^2 = 2.96, P > 0.05.

Observed indicators

Patients were followed up four weeks after treatment, and the ^{13}C urea breath test (^{13}C-UBT) was carried out to detect the presence of *H. pylori*.

Ethics

This was a clinical study carried out in humans, and the protocol for this work was approved by the Institutional Ethics Committee of the First Affiliated Hospital of Henan University of Science and Technology. Before the study began, the patients signed an informed consent form which included name, age, gender, chief complaint, drug history and past medical history.

Statistical analysis

The *H. pylori* eradication rate was assessed based on intention-to-treat (ITT) and per-protocol (PP) analysis. The 95%CI were also calculated for both the ITT and PP analyses and the eradication rate. The patients who were lost to follow-up or could not complete the treatment course due to severe adverse reactions, were considered treatment failures and were excluded in the PP analysis. The χ^2 test and Fisher's exact test were used to compare the differences between the two groups in terms of baseline data, eradication rate and adverse reactions. $P < 0.05$ was considered significant.

RESULTS

Treatment results

In the experimental treatment group, 7 of the 78 patients were lost to follow up (9%), and of the 71 remaining patients, 67 were negative by the ^{13}C-UBT. In the standard triple treatment group, 6 of the 69 patients were lost to follow up (8.6%), and of the remaining 63 patients, 46 were negative by the ^{13}C-UBT.

The eradication rate following the PP analysis in the experimental treatment group was 94.3% (67/71), and was 73% (46/63) in the standard triple treatment group. The eradication rate following the ITT analysis was 86%

Table 2 *Helicobacter pylori* eradication rate in the two groups

Group	Eradication	No eradication	Follow-up lost	Eradication rate[1] (PP) (95%CI)	Eradication rate[2] (ITT) (95%CI)
Experimental treatment group	67	4	7	94% (88%-99%)	86% (78%-94%)
Standard triple treatment	46	17	6	74% (64%-84%)	67% (57%-77%)

[1]χ^2 = 12.10, P < 0.05; [2]χ^2 = 7.615, P < 0.05. PP: Per-protocol; ITT: Intention-to-treat.

Table 3 *Helicobacter pylori* eradication rates in relation to disease *n* (%)

Group	Chronic erosive gastritis	Gastric ulcer	Duodenal ulcer
Experimental treatment	29 (34)	24 (28)	14 (16)
Standard treatment	21 (31)	11 (17)	14 (21)

χ^2 = 2.29, P > 0.05

and 67% in the two groups, respectively. The eradication rates in the two groups were statistically significant (P < 0.05) (Table 2). The eradication rate in patients with different diseases in the two groups was not significantly different (Table 3).

Side effects

Major adverse reactions were abdominal pain, dry mouth, dizziness, nausea, vomiting and bloating symptoms, however, these reactions were mild and well tolerated. All patients were able to complete the treatment regimen (Table 4).

DISCUSSION

Warren and Marshall reported the isolation of Campylobacter unidentified (unidentified curved bacilli) from the stomach in 1983, which was officially named *H. pylori* in 1989. *H. pylori* is considered to be the etiologic cause of gastritis, peptic ulcer disease and is associated with the development of gastric cancer[7-9]. It is a spiral or curved gram-negative microaerophilic flagellated bacillus. The prevalence of *H. pylori* infection varies worldwide, and depends on socioeconomic status and sanitation conditions[10]. The diagnosis of *H. pylori* can be performed using invasive and noninvasive methods. Invasive methods include the urease test, which has a sensitivity ranging from 79.7% to 97.5% and a specificity from 97.2% to 100%[11-14], it is performed in the endoscopy unit and is a suitable rapid indirect test to confirm the presence of *H. pylori* in biopsy samples. The urea breath test is considered the gold standard for the diagnosis of *H. pylori* infection, and has a sensitivity and a specificity ranging from 90% to 100%[15-18]. Therefore, we suggest using the ^{13}C-UBT, or esophagogastroduodenoscopy for the assessment of *H. pylori* status.

With increased research on bacteria and drug treatment trials for *H. pylori* infection, it is now clear that antibiotics, antacids, metal preparations and other drugs are effective. Antibiotics used in the treatment of *H. pylori* infection include amoxicillin, tetracycline, clarithromycin, quinolones, furazolidone, metronidazoles and other drugs which have either bactericidal or bacteriostatic effects. Antacids include PPIs and histamine2-receptor antagonists. PPI-clarithromycin-amoxicillin or metronidazole treatment for 7 to 14 d is the first treatment choice for *H. pylori* infection[19]. However, several large clinical trials and meta-analyses have shown that the eradication rate with standard triple therapy has generally declined to unacceptable levels (*i.e.*, 80% or less) recently[20,21].

With increasing clinical use of antibiotics, *H. pylori* resistance appears to have significantly increased. Abuse and irrational drug use as well as repeated anti-*H. pylori* treatment failure are important causes of drug resistance[22].

According to the *H. pylori* Study Group of Digestive Diseases Division of the Chinese Medical Association, which investigated multiple regions of the country in 2007, the resistance rates of *H. pylori* to metronidazole, clarithromycin and amoxicillin were 75.6%, 27.6% and 2.7%, respectively[23]. *H. pylori* resistance to antibiotics is the most important factor in treatment failure. Therefore, the choice of antibiotics is the key to successful eradication of *H. pylori*, in the absence of drug susceptibility testing, and it is safe to use the less frequently used antibiotics which are less likely to induce antibiotic resistance.

The mechanism of action of PPIs involve: (1) direct inhibition of the growth of *H. pylori*; (2) inhibition of urease activity; and (3) increased intragastric pH and enhanced antibiotic activity[24]. Hepatic oxidation is mediated by the cytochrome P450 2C19 (CYP2C19) gene which is polymorphic and produces fast metabolizers and low metabolizers. This is another important factor in the failure of *H. pylori* eradication therapy, and one study suggested that this is the second leading cause of bacterial resistance[25]. The elimination of omeprazole, lansoprazole and pantoprazole involves hepatic oxidation mediated by cytochrome CYP2C19 and CYP3A4, while that of rabeprazole involves its reduction *via* a non-enzymatic pathway to rabeprazole-thioether and partial metabolism by CYP2C19 and CYP3A4[21]. Thus, rabeprazole is less susceptible to the influence of genetic polymorphisms of either CYP2C19 or CYP3A4, and was found to depend only on its pharmacokinetic and pharmacodynamic characteristics. The pKa of rabeprazole is 5.0 and those of other PPIs, such as omeprazole and lansoprazole, are around 4.0, rabeprazole accumulates in an acidic space up to a concentration ten-fold greater than do other PPIs. In addition, rabeprazole is known to transform into the acid-activated form much faster than other PPIs, which further contributes to the inhibition of proton pumps immediately after the arrival of rabeprazole at the target site[26].

Levofloxacin is a third-generation fluoroquinolone, its antibacterial mechanism involves inhibition of bacterial type Ⅱ topoisomerase. Topoisomerase controls DNA to-

Table 4 Side effect profile of patients

Group	No adverse reactions	Abdominal pain	Nausea	Vomiting	Dry throat	Bloating	Dizziness	Total
Experimental treatment	58	8	10	6	4	5	7	40
Standard triple	55	7	6	5	3	2	1	24
Total episodes	113	15	16	11	7	7	8	64

$\chi^2 = 2.13$, $P > 0.05$.

pology in DNA replication and repair, it is a key enzyme in transcription. Levofloxacin, blocks DNA replication by inhibiting bacterial DNA gyrase A subunit and inhibits topoisomerase Ⅳ activity, thus has a bactericidal effect[27]. In addition, levofloxacin has no cross-resistance to *B*-lactam and macrolide antibiotics.

The clinical use of furazolidone is not very extensive, and it is not a commonly used drug in the standard regimen. However, it has a significant effect on *H. pylori* and does not tend to produce drug resistance. The reported furazolidone sensitivity rate is generally 100%[28], and it is inexpensive, therefore, we chose this medication for our *H. pylori* infected patients, and the results showed that inclusion of this drug in the quadruple regimen for *H. pylori* infection resulted in a high eradication rate, thus, this agent has good efficacy. The most common side effects of furazolidone are nausea, vomiting and other gastrointestinal reactions. In this study, gastrointestinal reactions were seen in patients taking furazolidone, however, multiple neuritis was not noted, and the drug was well tolerated.

In summary, these experimental results demonstrated that rabeprazole - amoxicillin - levofloxacin - furazolidone quadruple combination therapy is a safe, highly effective and well tolerated regimen for eradication of *H. pylori*.

COMMENTS

Background

Helicobacter pylori (*H. pylori*) eradication rates with standard triple therapy are declining worldwide. The optimal management of *H. pylori* is evolving and new treatment combinations for antibiotic resistant *H. pylori* strains are required.

Research frontiers

Standard triple therapy represents the accepted standard therapy for *H. pylori* as the organism is known to be susceptible to clarithromycin, and local antimicrobial resistance rates are below 20%, while newer treatment regimens (sequential, quadruple, concomitant and hybrid therapies) and various combinations of new and old antibiotics aimed at eradicating the organism more effectively are increasing in popularity.

Innovations and breakthroughs

In this study, the authors provide further evidence of the efficacy and tolerability of quadruple eradication therapy for *H. pylori* infection.

Applications

Empirical therapy can be employed to treat *H. pylori* infection if antimicrobial sensitivity data are unavailable.

Terminology

A 7-d quadruple therapy consisting of rabeprazole (20 mg *bid*) amoxicillin (1.0 g, *bid*) levofloxacin (0.2 g, *bid*) and furazolidone (0.1 g, *bid*), has high efficacy in the treatment of *H. pylori* infection with an eradication rate of 86% by intention-to-treat analysis and 94% by per-protocol analysis.

Peer review

This is a nice study, particularly for populations who have a relative high prevalence of CYP2C19 polymorphism. The article represents an important contribution to the treatment of *H. pylori*.

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