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BRIEF ARTICLE

Standard triple, bismuth pectin quadruple and sequential therapies for *Helicobacter pylori* eradication

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Abstract

AIM: To compare the effectiveness of standard triple, bismuth pectin quadruple and sequential therapies for *Helicobacter pylori* (*H. pylori*) eradication in a randomized, double-blinded, comparative clinical trial in China.

METHODS: A total of 215 *H. pylori*-positive patients were enrolled in the study and randomly allocated into three groups: group A (n = 72) received a 10-d bismuth pectin quadruple therapy (20 mg rabeprazole *bid*, 1000 mg amoxicillin *bid*, 100 mg bismuth pectin *qid*, and 500 mg levofloxacin *qd*); group B (n = 72) received the sequential therapy (20 mg omeprazole *bid*, 1000 mg amoxicillin *bid*, in 5 d, followed by 20 mg omeprazole *bid*, 500 mg tinidazole *bid*, 500 mg clarithromycin *bid*, for another 5 d); group C (n = 71) received a standard 1-wk triple therapy (20 mg omeprazole *bid*, 1000 mg amoxicillin *bid*, 500 mg clarithromycin *bid*). After all these treatments, 20 mg omeprazole *bid* was administrated for 3 wk. *H. pylori* status was assessed by histology, 13C-urea breath test and rapid urease test at baseline and 4-6 wk after completion of treatment. Ulcer cicatrization was assessed by gastroscopy. χ^2 test ($P < 0.05$) was used to compare the eradication rates and ulcer cicatrisation rates among the three groups.

RESULTS: The eradication rate was 83.33% (60/72) in group A, 88.89% (64/72) in group B, and 80.56% (58/71) in group C. The ulcer cicatrisation rate was 86.44% (51/59) in group A, 90.16% (55/61) in group B, and 84.91% (45/53) in group C. The sequential therapy yielded a higher eradication rate and ulcer cicatrisation rate than the standard triple and bismuth pectin quadruple therapies. Statistically, the eradication rate of group B was significantly different from groups A and C ($P < 0.05$), but the difference of ulcer cicatrisation rate and side effects was not statistically significant among the three groups ($P > 0.05$). The three protocols were generally well tolerated.

CONCLUSION: The sequential therapy has achieved a significantly higher eradication rate, and is a more suitable first-line alternative protocol for anti-*H. pylori* infection compared with the standard triple and bismuth pectin quadruple therapies.

Key words: *Helicobacter pylori*; Sequential therapy; Triple therapy; Bismuth pectin quadruple therapy; Eradication rate

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INTRODUCTION

Helicobacter pylori (H. pylori) infection habitually causes chronic active gastritis, which significantly enhances the risk for intestinal metaplasia in the stomach, and it is undoubtedly involved in gastric carcinogenesis. Moreover, *H. pylori* also play a crucial role in the pathogenesis of peptic ulcer and mucosa-associated lymphoid tissue lymphoma, including peptic ulcer complications, such as bleeding or stenosis[1-4]. According to the Maastricht 2 guidelines, the first-line treatment for *H. plori* eradication is the triple therapy using a proton-pump inhibitor (PPI) *bid*, 1 g amoxicillin *bid*, and 500 mg clarithromycin *bid*. In the case of penicillin allergy, 500 mg metronidazole *bid* is substituted for amoxicillin. After a decade of clarithromycin-based treatment and continued widespread use of long-acting macrolides in general practice, 10%-15% of *H. pylori* strains are resistant *de novo* to clarithromycin[3]. As a result, the failure rate is around 20% for the triple therapy (PPI plus amoxicillin plus clarithromycin)[4,5]. When the first-line *H. pylori* eradication treatment fails, a second-line treatment of quadruple therapy, with a PPI *bid*, colloidal bismuth subcitrate *qid*, 500 mg metronidazole *tid*, and 500 mg tetracycline *qid*, is recommended. Some recent studies have compared the efficacy of the triple *vs* quadruple therapy, and a meta-analysis has assessed these studies[6]. Eradication rates were not significantly different among patients receiving triple or quadruple therapy. The eradication rates in the patients receiving either triple or quadruple therapy in this study were almost similar to those obtained previously[4,7,8].

Clarithromycin and metronidazole resistance has increased substantially in recent years, and there has been a corresponding decrease in the eradication rate for *H. pylori* infection in most Western countries[4]. In China, recent nationwide multi-center studies have demonstrated that clarithromycin resistance increased to 27.6%, and metronidazole resistance is extremely common, the average resistance rate being 75.6%. Furthermore, combined clarithromycin-metronidazole cross-resistance was found in 85.1% of clarithromycin-resistance *H. pylori* strains. Eradication rates in most Western countries and China have declined to unacceptable levels. Therefore, Antibiotic resistance is the main cause of failure in *H. pylori* eradication and bata-lactamase produced by resistant *H. pylori* strains is a possible mechanism underlying the ineffectiveness of an amoxicillin-based triple or quadruple therapy[1].

Sequential therapy is a latest protocol for *H. pylori* eradication suggested by De Francesco *et al*[9]. Sequential therapy refers to the idea of adding more antibiotics to the treatment regimen but giving them in sequence rather than giving all 4 drugs together. Typically, this involves an initial 5-d therapy with a benign combination (e.g. 40 mg pantoprazole with 1 g amoxicillin *bid*) followed by 5 d of two more antibiotics plus a PPI (e.g. 500 mg clarithromycin and 500 mg tinidazole plus 40 mg pantoprazole *bid*). A subgroup data-analysis in a large, prospective, controlled multi-center study showed that the eradication rate of this "new" treatment was significantly higher than that of the clarithromycin-based treatment (82% *vs* 44%, $P < 0.0155$). Child, adult and elderly patients receiving this "new" treatment achieved a high eradication rate and had less adverse reactions[10,11].

To our knowledge, no data are available about the efficacy of a 7-d standard triple therapy, a 10-d bismuth pectin quadruple therapy and a 10-d sequential therapy in China. The present study aimed to compare the efficacy of a 7-d standard triple therapy, a 10-d bismuth pectin quadruple therapy and a 10-d sequential therapy; to further test whether the 10-d sequential therapy is able to increase the eradication rate compared with the 7-d standard triple therapy and 10-d bismuth pectin quadruple therapy; to observe the adverse reactions; and to evaluate the reliability, safety and efficacy of this treatment in China.

MATERIALS AND METHODS

Patients

This is a prospective, parallel, open-label, randomized study. The study population consisted of patients with dyspepsia defined as having pain or discomfort in the upper abdomen.

A total of 215 patients infected with *H. pylori* were enrolled. The patients were screened from 15 322 patients who underwent gastroscopy at the Endoscopy Center of Weihai Municipal Hospital from January 1, 2005 to December 31, 2009. Patients enrolled in the present study had not been previously treated for *H. pylori* infection. Patients were excluded if they were taking PPI, H2-receptor antagonists, bismuth preparations or antibiotics 4 wk before the study. Pregnant women, patients with antibiotic allergy or severe diseases of organs, neoplasm, serious complications of ulcers, and hepatic impairment or kidney failure were not enrolled. All the participants signed informed consent form.

H. pylori infection was assessed at entry. All patients underwent endoscopy with biopsies for histology (two samples from the antrum and two from the corpus) and a rapid urease test (one sample from the antrum) (CP-test, China). Patients were diagnosed to be *H. pylori*-positive if both tests were positive. Biopsy specimens were histologically detected for *H. pylori* by hematoxylin and eosin stain. In patients diagnosed with ulcers by gastroscopy, the diameter of ulcers must be between 5 mm and 3 cm, and number of ulcers must be no more than 2 in stomach and/or duodenum, except for those with a history of peptic ulcer before present illness. The post-eradication assessment was undertaken 4-6 wk after completion of the treatment (after the subsequent 3-wk course of PPI) using a 13C-urea breath test (Infai, Sofar, Italy). Citric acid (1.5 g) as a test meal and 13C-urea (75 mg) as a water solution were given to the patients after collection of a baseline sample by blowing through a disposable plastic straw into a 20-mL container; an additional breath sample was collected 30 min later. The breath samples were considered positive if there was a greater than five per 1000 of $13CO_2$ difference over baseline, according to the manufacturer's recommendations. Meanwhile, all patients

underwent endoscopy with biopsies for histology (two samples from the antrum and two from the corpus) and a rapid urease test (one sample from the antrum), and the healing of ulcers *vs* pre-therapy was observed.

Therapeutic regimens

In the center, patients were randomly assigned using a computer generated list to one of the following treatments: Group A (n = 72): A 10-d triple therapy with 20 mg rabeprazole *bid*, 1000 mg amoxicillin *bid*, 100 mg bismuth pectin *qid*, and 500 mg levofloxacin *qd*; Group B (n = 72): A sequential therapy with 20 mg omeprazole *bid*, 1000 mg amoxicillin *bid*, for 5 d, followed by 20 mg omeprazole *bid*, 500 mg tinidazole *bid*, 500 mg clarithromycin *bid*, for another 5 d; and Group C (n = 71): A standard triple therapy with 20 mg omeprazole *bid*, 1000 mg amoxicillin *bid*, 500 mg clarithromycin *bid*.

For each regimen, the PPI was prescribed at 30 min before meals, but all antibiotics were given after meals. Patients were asked to return to assess the compliance and estimate the adverse reactions at the end of the treatment. Side effects were evaluated using a structured questionnaire by personal interview.

Statistical analysis

The sample size was calculated based on available data in the literature. By hypothesizing a 95% eradication rate for the sequential regimen[12] and 80% for either the 7-d standard triple, 10-d sequential therapy or 10-d bismuth pectin quadruple therapy[13], it was calculated that all patients per treatment arm were needed to find a statistically significant difference with a level of $P < 0.05$ and a power of 0.85. The eradication rates and their 95% CIs were calculated for each treatment regimen. For all other variables, χ^2, Fisher's exact test and Student's t test were used as appropriate, and $P < 0.05$ was considered significant. The difference in the eradication rates among the three treatments was estimated. Before pooling those estimates, a Fisher's exact test was applied to investigate the heterogeneity between the differences.

RESULTS

Eradication rates

Two hundred and thirteen patients with *H. pylori* were enrolled in the study. As shown in Table 1, the three patient groups did not differ in age, sex, gastritis distribution and location and number of peptic ulcers in gastric mucosa. All patients completed the treatment. *H. pylori* infection was successfully cured in 60/72 (83.33%) with a 10-d bismuth pectin quadruple therapy, in 64/72 (88.89%) with the sequential therapy, and in 58/71 (80.56%) with the 7-d standard triple therapy, respectively. As shown in Table 2, the eradication rates achieved by the sequential therapy were significantly higher than that by both the 10-d bismuth pectin quadruple therapy and 7-d standard triple therapy, with significant differences ($P < 0.05$). The ulcer cicatrisation was successfully cured in 86.44% by the 10-d bismuth pectin quadruple therapy, in 90.16% by the sequential therapy, and in 84.91% by the 7-d standard triple therapy. As shown in Table 1, although the sequential therapy tended to give better results in eradication rates when compared with the 10-d bismuth pectin quadruple therapy and 7-d standard triple therapy, no statistically significant difference was found ($P > 0.05$).

Table 1 Demographic and clinical characteristics of patients at entry into each treatment group

Patient characteristics (n)	Group A	Group B	Group C
Number of patients	72	72	71
Sex (M/F)	31/41	35/37	34/37
Age (yr), mean ± SD	45 ± 10	47 ± 13	43 ± 15
Antral gastritis	58	61	57
Pangastritis	17	15	19
Intestinal metaplasia	19	21	17
Duodenitis	11	13	10
Gastric ulcer	40	42	39
Duodenal bulb ulcer	13	12	10
Compound ulcers	6	7	4

Table 2 Eradication and ulcer cicatrisation rates in each treatment group

	Group A	Group B	Group C
Eradication rate (%)[a]	83.33 (60/72)	88.89 (64/72)	80.56 (58/71)
Ulcer cicatrisation rate (%)[b]	86.44 (51/59)	90.16 (55/61)	84.91 (45/53)

[a]$P < 0.05$, Group B *vs* Group C, Group A; [b]$P > 0.05$, Group B *vs* Group C, Group A.

Compliance and side effects

Compliance with the therapy was good (greater than 95% of prescribed drugs). Six patients (16.67%) treated with the 10-d bismuth pectin quadruple therapy complained of side effects (three with abdominal discomfort, two with abdominal pain, four with nausea/vomiting, two with parageusia and one with glossitis). Fourteen patients (19.44%) receiving the sequential therapy reported side effects (five with abdominal pain, one with constipation, two with parageusia, three with nausea/vomiting and three with pruritus). Eleven patients (15.49%) receiving the 7-d standard triple therapy complained of side effects (one with diarrhea, four with abdominal pain, one with parageusia, one with glossitis and three with nausea/vomiting). No statistically significant difference in the incidence of side effects was found among the three groups ($P > 0.05$). All side effects were self-limiting after the therapy was ended.

DISCUSSION

Since antibacterial activity of the majority of antibacterials decreases under intragastric low pH and the slime layer may prevent the drugs penetrating fully into the depth of the biofilm, *H. pylori* is not easily eliminated and can develop resistance to antimicrobial drugs. It is extremely important that a protocol with a high eradication rate should

be selected to ensure a successful eradication of *H. plori* in the treatment of peptic ulcers. At present, triple therapies suggested by either Canadian or European guidelines are the most preferred first-line protocols in clinical practice[2,14]. The proposal is being used by 85%, 84% and 67% of primary-care physicians in Italy, Israel and the United States, respectively[7,15,16]. However, the eradication rates substantially decreased by the triple therapy in several countries. Indeed, a success rate of less than 80% has been found in several European and Asian countries, the United States and Canada[17-25]. Eradication rate was extremely low (25%) in a recent study[26]. The resistance to clarithromycin and/or metronidazole is the primary cause of the descending *H. pylori* eradication rate[8,27,28]. In order to reinforce the curative effect of the standard triple therapy, some scholars suggest that the duration of the treatment may be extended to 14 d. One meta-analysis suggests that the 14-d triple therapy can increase the *H. pylori* eradication rate by 12% compared with the 7-d therapy, but the expenditures increase simultaneously. Therefore, it is imminent to seek a new eradication strategy.

Sequential therapy is a recent proposal for *H. pylori* eradication suggested by Zullo *et al*[29]. De Francesco found that double drugs administration for 14 d and subsequent triple drugs for 7 d significantly increased the eradication rate (97.3%) compared with the proposal of converse administration (81.6%, triple drugs administration for 7 d and subsequent double drugs for 14 d). It suggests that the sequence of antibiotic administration affects the *H. pylori* eradication. Zullo *et al*[30], Sánchez-Delgado *et al*[31] and Zullo *et al*[32] further simplified this proposal, and named it sequential therapy. Sequential therapy refers to the idea of adding more antibiotics to the treatment regimen but giving them in sequence rather than giving all 4 drugs together. Typically, this involves an initial 5-d therapy with a benign combination (40 mg pantoprazole and 1 g amoxicillin *bid*) followed by 5 d of two more antibiotics plus a PPI (500 mg clarithromycin and 500 mg tinidazole plus 40 mg pantoprazole *bid*). Subgroup data analysis in a large, prospective, controlled multi-center study showed that the eradication rate of this "new" treatment was significantly higher compared with the clarithromycin-based treatment (82% *vs* 44%, $P < 0.0155$). Child, adult and elderly patients receiving this "new" protocol all achieved a high eradication rate and had less adverse reactions[10,11].

This study compared the effectiveness among sequential therapy, triple therapy, and Bismuth Pectin quadruple therapy for *H. pylori* eradication. *H. pylori* was eradicated effectively in all groups, with a success rate of over 80% that was consistent with the standards of Maastricht and other guidelines. Sequential therapy reached an eradication rate of 88.89%, with significant differences compared with other therapies ($P < 0.05$), but the healing rate of ulcers was not significantly different ($P > 0.05$) among the three groups. It was basically the same as the previous publications. Sequential therapy (omeprazole, clarithromycin, amoxicillin plus tinidazole are administrated in sequence for 10 d) has several advantages: the treatment duration is appropriately increased. Amoxicillin acts on the cell wall of bacteria in the first 5-d treatment to prevent clarithromycin pathway formation, thus increasing the sensitivity of the bacteria to clarithromycin, and effectively avoiding the *collateral resistance to* clarithromycin. Omeprazole, clarithromycin plus tinidazole are administrated for the remaining 5-d treatment. Clarithromycin acts on bacterial nucleic acid, restrains protein synthesis, stabilizes in acid environment, and increases the synergetic effects of the drugs and the cure rate of *H. pylori* infection.

Resistance to metronidazole and clarithromycin is the main reason for treatment failure of eradicating *H pylori*[33].

Early documents generally demonstrated that *H. pylori* primary resistance to clarithromycin is very low and usually not more than 10%. But for the past a few years, following the wide use of clarithromycin, *H. pylori* resistance to clarithromycin has gradually increased, so did the nitroimidazoles, and cross-resistance has also appeared. In China, the recent nationwide multi-center studies[34] have demonstrated that the resistance to clarithromycin increased to 27.6%, and resistance to metronidazole reached 75.6%. Furthermore, cross-resistance to metronidazoles appeared in 85.1% of clarithromycin-resistant *H. pylori* strains. It suggests that *H. pylori* resistance to clarithromycin and metronidazoles is an extremely serious problem. As resistance to clarithromycin also increased in Western countries, there has been a corresponding decrease in the eradication rate for *H. pylori* infection[4]. A study in Italy[35] presented that in the past 15 years, resistance to clarithromycin doubled from 10.2% in 1989-1990 to 21.3% in 2004-2005. But the resistance rate to metronidazole in adult is 10%-50% in Western countries and 77%-95% in developing countries[36]. The eradication rate of the sequential therapy in this study (88.89%) is lower than in Western countries (over 90%). According to the known mechanism of the proposal, it only improves the *H. pylori* sensitivity and prevents collateral resistance to clarithromycin. As resistance to metronidazole is extremely common in China, it has decreased the *H. pylori* eradication rate of the protocol.

Therefore, antibiotic resistance is the main cause of failure in *H pylori* eradication and beta-lactamase produced by resistant *H. pylori* strains is a possible mechanism underlying the ineffectiveness of an amoxicillin-based triple or quadruple therapy[1].

In short, the 10-d sequential therapy is significantly dominant compared with standard triple and bismuth pectin quadruple therapy, and adverse effects are not significantly different ($P > 0.05$). Therefore, the sequential therapy is a better choice of treatment for *H. pylori* eradication. But further researches are needed to formulate the strategies of sequential therapy and probe into the exact mechanism of eradicating *H. pylori*.

COMMENTS

Background

Clarithromycin and metronidazole resistance has increased substantially in recent years, and there has been a corresponding decrease in the eradication

rate for *Helicobacter pylori* (*H. pylori*) infection in most Western countries and China. Sequential therapy is a recent protocol for *H. pylori* eradication.

Research frontiers

To the authors' knowledge, no data are available about the efficacy of a 7-d standard triple therapy, a 10-d bismuth pectin quadruple therapy and a 10-d sequential therapy in China. The present study aimed to compare the efficacy of a 7-d standard triple therapy, a 10-d bismuth pectin quadruple therapy and a 10-d sequential therapy in China.

Innovations and breakthroughs

The results denote that the 10-d sequential therapy is significantly dominant compared with standard triple and bismuth pectin quadruple therapy, and adverse effects are not significant different. The eradication rate of the sequential therapy in this study (88.89%) is lower than in Western countries (over 90%). As resistance to metronidazole and clarithromycin is extremely more common in China than in Western countries, it has decreased the *H. pylori* eradication rate of the therapy.

Applications

Sequential therapy is a better choice of treatment for *H. pylori* eradication in China. It may be suggested as the first-line protocol for eradicating *H. pylori*. Therefore, it may increase the eradicate rate, decrease the resistance to antibiotics, then decrease the prevalence of *H. pylori*-related diseases. However, the strategies of sequential therapy need further studies to fit for the situation of China.

Terminology

Sequential therapy refers to the idea of adding more antibiotics to the treatment regimen, but giving them in sequence rather than giving all 4 drugs together. Typically, this involves an initial 5-d therapy with a benign combination of drugs, followed by 5 d of two more antibiotics plus a proton-pump inhibitor.

Peer review

This is an interesting study that provides further strong support for sequential therapy being superior to other regimens. The study appears to have been designed well, but some details of the design and study structure are absent.

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