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ORIGINAL ARTICLE

Case Control Study

Seven-day triple therapy is a better choice for *Helicobacter pylori* eradication in regions with low antibiotic resistance

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Abstract

AIM: To investigate whether 7-d triple therapies are still valid in populations with low levels of resistance.

METHODS: A total of 1106 *Helicobacter pylori* (*H. pylori*)-positive patients were divided into three groups, each of which received one type of 7-d triple therapy. Therapeutic outcomes of the patients were assessed by the ^{13}C-urea breath test at 8 wk after treatment. The susceptibility of *H. pylori* to antibiotics was determined by an agar-dilution method. Data analysis was performed by χ^2 tests.

RESULTS: The eradication rates in groups A, B and C were 90.71% (332/366), 90.46% (313/346) and 90.87% (189/208), respectively (P = 0.986). The resistance rates were 8.91% for clarithromycin, 14.78% for levofloxacin and 0% for amoxicillin. The eradication rate was significantly different between clarithromycin- and levofloxacin-resistant patients (P < 0.05) in group A. Patients whose treatment failed in group A also had a higher clarithromycin resistance rate than did successive patients (P = 0.034). However, levofloxacin resistance had no obvious influence on the eradication rate. Furthermore, three main antibiotics (clarithromycin, levofloxacin and amoxicillin) had lower DID (defined daily dose per 1000 inhabitants per day) in this city.

CONCLUSION: Clarithromycin resistance is the main reason for the failure of 7-d triple therapy. In populations with low levels of resistance, a 7-d triple therapy is a viable choice. The choice of therapy should not be influenced by conditions in high antibiotic resistance regions.

Key words: *Helicobacter pylori*; Seven-day triple therapy; Eradication rate; Clarithromycin resistance; Levofloxacin resistance

Core tip: A major cause of treatment failure for *Helicobacter pylori* (*H. pylori*) infections is the increasing rate of antibiotic resistance. A total of 1106 *H. pylori*-positive patients were treated with one of three types of 7-d triple therapies. The results of the ^{13}C-urea breath test during patient follow-up indicated that the eradication rates were greater than 90%. The susceptibility of all *H. pylori* strains to four antibiotics was determined using an agar-dilution method. We found that the eradication rate was significantly different in antibiotic-resistant patients. In populations with low levels of resistance, 7-d triple therapy is a better choice.

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INTRODUCTION

Since the discovery of *Helicobacter pylori* (*H. pylori*), many studies have been carried out with the goal of improving *H. pylori* eradication and therapies have changed from single-antibiotic treatments to the current multi-antibiotic treatments[1-6]. However, the eradication rate of *H. pylori* is still less than 80%[6]. The reasons for this low eradication rate are likely to be multifactorial, including the reduced activity of antimicrobial drugs with an acidic pH or poor patient compliance[2,7]. The increasing rate of antibiotic resistance of *H. pylori* has attracted a great deal of attention, especially clarithromycin resistance[6-9]. In most countries, clarithromycin resistance has exceeded the minimum value (15%) of the Maastricht IV consensus recommendation; for example, the rates of clarithromycin resistance are 28% in Japan and 38.5% in South Korea[10-12]. In the southeast coastal region of China, the rate of clarithromycin resistance has reached 21.5%[13].

At present, triple therapy is commonly used as a first-line treatment regimen for *H. pylori* eradication in most countries. However, due to increased antibiotic resistance and regional differences in antibiotic resistance, the standard triple therapy has been changed. To obtain a higher eradication rate, especially in cities where antibiotic resistance is a serious problem, the standard 7-d therapy has been extended to 10 d, 14 d or even longer[14-16]. Furthermore, some studies have suggested the use of an alternative antibiotic regimen, such as the replacement of clarithromycin with levofloxacin or tetracycline. Unfortunately, the eradication rate has still been unsatisfactory[17,18]. Recently, individualized therapy has been recommended in some regions to solve some difficult problems caused by *H. pylori* resistance to antibiotics. However, in low-resistance groups and in people who are sensitive to antibiotics, traditional therapies, such as the 10-d or 14-d triple therapy, are still applied as current treatment strategies[19]. Therefore, valid data are needed to guide clinical practice when considering the problem of individualized therapy and low resistance groups.

China is a developing country, and urbanization in rural areas has increased with rapid economic growth. Furthermore, the new cooperative medical scheme in China has provided more urban-type medicine to rural areas[20]. Although there are significant differences in available medications and antibiotic resistance between rural and urban regions, urban treatment strategies are generally applied in all regions. Recently, three types of first-line 7-d triple therapies were tested for the clinical treatment of *H. pylori* infections in Yongkang City, Zhejiang Province, China, which typically has a population with a low antibiotic resistance rate, and a higher eradication rate was achieved. This study provides a clinical reference for treatment strategies in similar regions.

MATERIALS AND METHODS

Patient selection

From March 2013 to December 2013, patients with upper gastrointestinal symptoms at the First People's Hospital of Yongkang, Zhejiang Province, China were enrolled in the study. During endoscopies, gastric mucosa biopsy samples from the antrum were collected to isolate *H. pylori* strains. Written informed consent was obtained from all patients, and this study was approved by the Ethics Committee of the National Institute for Communicable Disease Control and Prevention of the Chinese Center for Disease Control and Prevention.

Identification of H. pylori-positive patients

All of the gastric mucosa biopsy samples collected from patients, which were preserved in a brain-heart infusion broth, were sent to a laboratory at the Hangzhou Zhiyuan Medical Inspection Institute. The isolation and identification of *H. pylori* strains were performed as described previously[21]. Briefly, a gastric mucosa biopsy sample was grinded and inoculated directly onto a Columbia Agar (Oxoid, Hampshire, United Kingdom) plate containing 5% defibrinated sheep blood. The plate was incubated under microaerophilic conditions (5% O_2 and 10% CO_2) for 3 d at 37 ℃. Translucent colonies were identified by colony morphology after Gram staining. Spiral Gram-negative strains that were positive for urease, catalase and oxidase activity were identified as *H. pylori*-positive samples. For this study, a total of 1106 consecutive *H. pylori*-positive patients were chosen.

Treatment design and analysis of therapeutic outcomes

Study patients were divided into three groups according to their visit dates. Patients seen on a Monday or Thursday were assigned to group A, patients seen on a Tuesday or Friday were assigned to group B and patients seen on a Wednesday or Saturday were assigned to group C. The selection bias could not be completely eliminated, but met the random sampling criteria for statistical analysis. We made treatment plans for this study based on effective treatment for *H. pylori* eradication described in the literature[22,23]. All patients received 7-d triple therapy (group A: omeprazole 20 mg b.i.d., clarithromycin 500 mg b.i.d., and amoxicillin 1 g b.i.d.; group B: omeprazole 20 mg b.i.d., levofloxacin 400 mg b.i.d., and amoxicillin 1 g b.i.d.; group C: rabeprazole10 mg b.i.d., levofloxacin 400 mg b.i.d., and amoxicillin 1 g b.i.d.).

The outcomes of 7-d triple therapy were assessed by ^{13}C-urea breath tests. Eight weeks after treatment, a ^{13}C-urea breath test was performed on patients as a follow-up; 100 mg ^{13}C-urea was used, and analysis was carried out with a modified isotope ratio mass spectrometer to determine the $^{13}CO_2$ content[24]. A negative result from the ^{13}C-urea breath test was defined as successful eradication of *H. pylori*.

Antibiotic susceptibility test

Susceptibility of all 1106 *H. pylori* strains to four antibiotics, *i.e.*, clarithromycin, levofloxacin, amoxicillin and metronidazole, was determined using an agar-dilution method[25]. The following breakpoints were applied: clarithromycin $\geqslant$ 1, levofloxacin $\geqslant$ 2, amoxicillin $\geqslant$ 2, and metronidazole $\geqslant$ 8 μg/mL[25,26]. Briefly, 2 μL suspensions of *H. pylori* strains were aseptically inoculated onto Mueller-Hinton agar (Oxoid) plates containing 5% sheep blood and a single antibiotic and then incubated in a microaerophilic environment (5% O_2, 10% CO_2 and 85% N_2) at 37 ℃ for 3 d. Antibiotic resistance was determined if *H. pylori* growth was observed from a single inoculation after culturing. The reference strain ATCC43504 was used in the susceptibility test and all of the tests were repeated.

Local antibiotic consumption

Data on clarithromycin, levofloxacin and amoxicillin consumption in 2013 were investigated. Statistical results were expressed as the defined daily dose (DDD) per 1000 inhabitants per day (DID)[27].

Statistical analysis

Data analysis was performed by χ^2 tests using the SPSS software package (version 17.0; SPSS, Inc., Chicago, IL, United States). A P-value < 0.05 was considered to be significant.

RESULTS

Characteristics of patients

A total of 1106 *H. pylori*-positive patients were enrolled in this study. Endoscopic diagnoses and other demographic data are shown in Table 1; the male-to-female ratio was 1:0.93, and the mean age of the patients was 53.28 ± 12.54 (range, 2-84 years). A total of 920 patients visited their physicians again for a follow-up, including 366 from group A, 346 from group B, and 208 from group C. The rate of loss to follow-up in this study was 16.82% overall, and the rates for groups A, B and C were 18.18% (85/451), 15.82% (65/411), and 14.75% (36/244), respectively.

H. pylori eradication

According to the results of the ^{13}C-urea breath tests performed after 8 wk of treatment, the pre-protocol (PP) analysis showed that *H. pylori* eradication was successful for 90.65% (834 of 920) of the participants in this study. The eradication rates in groups A, B and C were 90.71% (332 of 366), 90.46% (313 of 346) and 90.87% (189 of 208), respectively. There were no significant differences in the *H. pylori* eradication rates among the three groups (χ^2 = 0.027, P = 0.986).

Table 1 Demographic data of patients in this study

	Patients (n = 1106)	Follow-up patients (n = 920)
Gender		
Male	572	486
Female	534	434
Age		
⩽ 10	1	1
11-20	3	1
21-30	54	51
31-40	146	127
41-50	214	183
51-60	321	281
61-70	314	239
71-80	49	35
81-90	4	2
Endoscopic diagnosis		
Superficial gastritis	302	246
Atrophic gastritis	24	22
Reflux gastritis	35	31
Erosive gastritis	597	504
Gastric ulcer	28	22
Ulcer of gastric fundus	1	1
Ulcer of gastric antrum	8	8
Ulcer of gastric angle	6	4
Duodenal ulcer	72	57
Gastroduodenal ulcer	30	23
Other	3	2

Table 2 Antimicrobial susceptibility testing in *Helicobacter pylori* strains n (%)

Antibiotic	Resistant isolates of each group in follow-up patients			
	Total (n = 920)	A group (n = 366)	B group (n = 346)	C group (n = 208)
CLR	82 (8.91)	29 (7.9)	30 (8.67)	23 (11.06)
LVX	136 (14.78)	54 (14.75)	50 (14.45)	32 (15.38)
MTZ	881 (95.76)	354 (96.72)	330 (95.38)	197 (94.71)
MTZ + CLR	79 (8.59)	28 (7.65)	29 (8.38)	22 (10.58)
MTZ + LVX	131 (14.24)	52 (14.21)	49 (14.16)	30 (14.42)
CLR + LVX	39 (4.24)	9 (2.50)	13 (3.76)	17 (8.17)
MTZ + CLR + LVX	37 (4.02)	9 (2.50)	12 (3.47)	16 (7.69)

CLR: Clarithromycin; LVX: Levofloxacin; MTZ: Metronidazole; AMX: Amoxicillin.

Table 3 Eradication rates of groups A, B and C in antibiotics resistant and susceptible patients n (%)

	Group A	Group B	Group C
CLR resistance	23 (79.31)	28 (93.33)	21 (91.30)
CLR susceptibility	308 (91.39)	285 (90.19)	168 (90.81)
LVX resistance	51 (94.44)	46 (92.00)	30 (93.75)
LVX susceptibility	281 (90.01)	267 (90.20)	159 (90.34)

Antimicrobial susceptibility

To better explain the higher eradication rate of *H. pylori* infections, four antibiotics including clarithromycin, levofloxacin, amoxicillin and metronidazole were chosen to perform susceptibility tests in patients during the follow-up (Table 2). The susceptibility tests showed that the resistance rates of *H. pylori* were 8.91% (82/920) for clarithromycin, 14.78% (136/920) for levofloxacin, and 0% for amoxicillin. In contrast, the rate of metronidazole resistance was maintained at a constant high level (95.76%), but did not affect the higher eradication rate in the Yongkang populations. The clarithromycin resistance rates were 7.9%, 8.67% and 11.06% in groups A, B and C, respectively (χ^2 = 1.645, P = 0.439). For levofloxacin, the resistance rates were 14.75%, 14.45% and 15.38% in groups A, B and C, respectively (χ^2 = 0.090, P = 0.956).

Comparative analysis of eradication rate and antibiotics resistance

As shown in Table 3, the eradication rates in clarithromycin-susceptible, clarithromycin-resistant, levofloxacin-susceptible and levofloxacin-resistant patients were displayed in groups A, B and C separately. In group A, the eradication rates in clarithromycin-resistant and clarithromycin-susceptible patients were significantly different (χ^2 = 4.509, P = 0.036). Levofloxacin resistant patients in group A showed a significantly higher eradication rate than patients with clarithromycin resistance (χ^2 = 4.470, P = 0.034). Furthermore, patients in group A whose eradication failed (17.14%, 6/35) showed a higher clarithromycin resistance rate (χ^2 = 4.509, P = 0.034) than patients with eradication success (6.95%, 308/331). These findings suggest that clarithromycin resistance was a key factor for eradication failure, and levofloxacin resistance did not affect the higher eradication rate in group A. In groups B and C, the levofloxacin resistance rates were 15.14% (76/502) in patients whose eradication was a success and 11.54% (6/52) in patients whose eradication failed (χ^2 = 4.485, P = 0.486). However, in groups B and C, there were higher eradication rates of *H. pylori* infection (P > 0.05), even with clarithromycin or levofloxacin resistance.

Antibiotic consumption

Data from 2013 in the city of Yongkang showed that outpatient use of antibiotics was 2.77 DID. Three main antibiotics in this study had low DID values; clarithromycin was the most commonly used (0.369 DID, 13.3% in 2013), amoxicillin was the least used (0.124 DID, 4.48% in 2013) and levofloxacin had a usage rate of 0.193 DID (6.97% in 2013). Lower DID values in the city of Yongkang determined the local prevalence of *H. pylori* resistance, which may be related to the higher eradication rates of *H. pylori* observed in this study.

DISCUSSION

With an increasing proportion of patients exhibiting antibiotic resistance to *H. pylori*, especially clarithromycin resistance, the efficacy of standard triple therapy has decreased in the last decades and has

fallen below 80% in several countries[6]. Although alternative first-line antibiotic treatments can achieve higher *H. pylori* eradication rates, they are still unsatisfactory because antibiotic use and resistance are increasing[17,18]. In this study, *H. pylori*-positive patients in Yongkang received three different types of 7-d triple therapies, and eradication rates greater than 90% were achieved, which was a grade B result (90%–94% success rate) in *H. pylori* therapy[28].

A good cumulative eradication rate is associated with low antibiotic resistance and better patient compliance[22]. In this study, antibiotic use was only 2.77 DID in Yongkang in 2013, and this low antibiotic use affected the local antibiotic resistance pattern. The rates of clarithromycin and levofloxacin resistance in this region were lower than 15%-20% (Table 2) as recommended by the Maastricht IV consensus[28]. In other words, Yongkang is a region with a low incidence of antibiotic resistance, which is the main reason for a local high rate of *H. pylori* eradication.

Study results from a region of low antibiotic resistance in Yongkang showed that all three types of triple therapy achieved a *H. pylori* eradication rate greater than 90%. A similar trend was found in other countries with a low incidence of resistance, but the treatment efficacies had significant differences. For example, in Germany, primary resistance was only 6.9% for clarithromycin, and patients suffering from peptic ulcer disease had a higher eradication rate than patients with normal mucosa (88.7% *vs* 70.1%, $P < 0.01$)[29]. In Hong Kong, the rates of resistance to clarithromycin and levofloxacin were low, and the eradication rate achieved by clarithromycin-based triple therapy was higher than that achieved by levofloxacin-based triple therapy (92.7% *vs* 85.3%, $P = 0.043$)[22,30]. In this study, there were no significant differences in *H. pylori* eradication rates between the treatment groups ($P = 0.986$), and the eradication rates were also not significantly different between gastritis (90.78%, 729/803) and ulcer disease (89.56%, 103/115) ($P > 0.05$). Therefore, three different triple therapies in Yongkang may permit a more comprehensive analysis of *H. pylori* eradication compared with first-line treatments in other regions.

Clarithromycin resistance to *H. pylori* is the main reason for the failure of standard triple therapy[31]. In group A, compared with the higher eradication rates observed in clarithromycin-susceptible patients (91.39%) and levofloxacin-resistant patients (94.44%), the eradication rate of clarithromycin resistant patients was only 79.31% ($P < 0.05$) (Table 3). Furthermore, patients for whom eradication failed had a significantly higher clarithromycin resistance rate (17.14% *vs* 6.95%, $P = 0.034$). In this study, groups B and C obtained eradication rates of over 90% in all patients. Therefore, in a region with a low incidence of antibiotic resistance, patients for whom eradication failed with standard triple therapy could choose other triple therapies based on antibiotic resistance patterns; for example, a levofloxacin-containing regimen could be used as an alternative first-line treatment. In contrast, levofloxacin resistance may not be a key factor in the eradication of *H. pylori* in regions with a low incidence of resistance, and medication compliance may influence eradication rates.

Because *H. pylori* resistance rates have continued to increase in recent decades, first-line treatments for *H. pylori* have evolved from the standard triple therapy to quadruple therapy or sequential therapy. Furthermore, the conventional 7-d therapy has been extended to 10 d, 14 d or even longer[14-16]. Indeed, to some extent, a longer duration of treatment improved the eradication rate, especially in regions with a high incidence of antibiotic resistance, but they cause more side effects and are a waste of resources[32]. Compared with the longer 10- or 14-d triple therapies, approximately 5%-8% patients for whom eradication failed with 7-d triple therapy received further tests and treatments[14,32]. However, 7-d triple therapy has greatly reduced the use of antibiotics and achieved a grade B (90%) eradication result[28]. From the perspective of health economics, the 7-d triple therapy is more suitable than longer triple therapies in regions with a low incidence of antibiotic resistance. Therefore, a 7-d triple therapy should be recommended in regions with a low incidence of antibiotic resistance, and individualized therapy should be considered. Therefore, in regions such as China, where *H. pylori* antibiotic resistance is significantly different between different populations, it is very important to carry out population-based antibiotic resistance detection and monitoring before an *H. pylori* eradication scheme is recommended.

COMMENTS

Background

Treatments for *Helicobacter pylori* (*H. pylori*) infections have been developed during the last 30 years. However, due to the increasing rate of *H. pylori* antibiotic resistance, the eradication rate has dropped below 80% in some regions of high antibiotic resistance. The standard 7-d therapy has also been extended to regimens of 10 d, 14 d or even longer. Although this strategy has improved the eradication rate of *H. pylori* to some extent, the longer treatment causes more side effects and is a waste of resources, especially in regions where there is a low incidence of antibiotic resistance. Therefore, there is a need to investigate whether 7-d triple therapies are still valid in populations with low levels of resistance.

Research frontiers

Since the discovery of *H. pylori*, its eradication rate has always been a concern. However, the success rate of treatment fails to exceed 80% in some studies. In this study, the authors performed three different types of 7-d therapies, and the *H. pylori* eradication rate was over 90%, which provides a reference for similar regions.

Innovations and breakthroughs

This study is the first one to investigate the relationship between the eradication rate of *H. pylori*, 7-d therapies and local antibiotic consumption in populations with low levels of resistance in China. This study demonstrated that 7-d triple therapy is a viable choice in regions of low antibiotic resistance and that clarithromycin resistance is the main reason for the failure of 7-d triple therapy.

Applications

This study suggested that it is very important to carry out antibiotic resistance detection and monitoring in populations before an *H. pylori* eradication scheme is employed and showed that 7-d triple therapy is a better choice in populations with low levels of resistance.

Terminology

This study suggested that it is very important to carry out antibiotic resistance detection and monitoring in populations before an *H. pylori* eradication scheme is employed and showed that 7-d triple therapy is the best choice in populations with low levels of resistance.

Peer-review

This study shows that eradication regimens should be based on the best locally effective regimen, ideally using individual susceptibility testing, community antibiotic susceptibility, or antibiotic consumption data and clinical outcome data. The study results are not only interesting for the Zhejiang Province of China but also for other areas with populations exhibiting low levels of resistance.

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