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Original Article

New Sequential Versus Triple Treatment Schedules for *Helicobacter pylori* Eradication in Iran

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ABSTRACT

Background :

Selection of the best approach for the treatment of *Helicobacter pylori (H. pylori)* infection that encompasses higher eradication and lower failure rates leads to a decline in its related complications and disorders. To understand the relative efficacy of new sequential therapy compared with standard triple therapy as two common regimens, we have performed a randomized, controlled trial to compare these two treatment protocols in an Iranian population.

Materials and Methods :

This study enrolled 220 patients aged 18-81 years old with dyspepsia or peptic ulcers who were candidates for endoscopy and referred to Taleghani Hospital, Tehran, Iran. Patients were randomized to receive one of two treatment regimens, a 14-day new sequential therapy that consisted of omeprazole (20 mg), amoxicillin (1.0 g), and ciprofloxacin (500 mg) administered twice daily for the first seven days, followed by omeprazole (20 mg), amoxicillin (1.0 g), and furazolidon (200 mg) administered twice daily for the remaining seven days. The second regimen comprised a proton pump inhibitor (PPI)-based triple therapy of omeprazole (20 mg), amoxicillin (1.0 g), and clarithromycin(500 mg) administered twice daily for 14 days.

Results :

Overall, 10 patients in PPI-based triple therapy group and 16 patients in the 14-day new sequential group stopped treatment and did not undergo 13C-urea breath testing (UBT). Among the remaining patients, the eradication rate with the PPI-based triple therapy was 89.0%, whereas it was 91.5% with the 14-day new sequential therapy which was not significantly different. No significant differences were found in eradication rates between genders in each treatment group. Adverse effects were mainly mild and comparable between the two treatment regimens.

Conclusion :

It seems that sequential regimen is at least as effective as standard therapy and can be used as an alternative treatment for *H pylori* eradication.

Keywords : *Helicobacter pylori*; Eradication; Side effects; New sequential therapy

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INTRODUCTION

Helicobacter pylori (H. pylori) infection is a leading cause of peptic ulcer disease, chronic gastritis, gastric adenocarcinoma and even mucosal-associated lymphoid tissue lymphoma (MALT). Selection of the best drug regimens for effective eradication of *H. pylori* infection, especially in patients at risk for peptic ulcer relapse and the development of complications of peptic ulcer disease remain challenging.

Despite the decrease in prevalence of *H. pylori* infection in many parts of the world, the frequency of *H. pylori* and its relation to peptic ulcer disease, gastric malignancy, and dyspeptic symptoms remain considerably high(1). In Iran, the prevalence of *H. pylori* infection has been estimated at 69% among healthy 18-65 year-olds and 25% in healthy children(2,3). *H. pylori* eradication is of importance for gastroesophageal cancer control in these populations(4). However, the high prevalence of antimicrobial drug resistance to this infection among high risk groups results in disease progression and also leads to continual damage to the gastric structure and its function. Thus this infection is difficult to cure, and generally necessitates the use of multi-drug therapy.

Triple-therapy that consists of an anti-secretory drug in addition to the combination of amoxicillin and clarithromycin, amoxicillin and metronidazole, or clarithromycin and metronidazole has been the standard treatment for *H. pylori* infection, which seems to provide appropriately consistent cure rates(5). However, some studies have shown a notable decline in eradication along with high failure rates of this triple-drug regimen in nearly one quarter of all patients(6,7). In some trials, eradication rates with standard triple-therapy have fallen from > 90% to 75–80% in some areas(8). It is believed that the widespread use of antibiotics has led to this dramatic increase in drug resistant strains.

Sequential therapy is another novel promising therapeutic approach that includes a proton pump inhibitor (PPI) plus amoxicillin followed by triple therapy for the remaining treatment duration(9). According to recent findings, it has been suggested that sequential therapy appears superior to a standard triple-drug regimen that contains a PPI and clarithromycin, in combination with either amoxicillin or an imidazole for different periods administered between 7 and 14 days(10). However, other studies have shown that the sequential therapy regimen failed to achieve higher eradication rates when compared with triple therapy(11-13). It is believed that the success rate of sequential therapy for *H. pylori* eradication depends on different factors such as variations in the resistant rate to commonly administered antibiotics among different populations(14).

To understand the relative efficacy of a 14-day new sequential therapy regimen compared with standard PPI-based triple therapy, we have performed a randomized, controlled trial to compare these two treatment protocols in an Iranian population.

As clarithromycin is expensive and its resistance rate approaches 17% in Iran, we have decided to choose another relatively low cost drug with less resistance for this study. Considering the relative low resistance rate of furazolidon and the poor tolerability of this drug over an extended period (two weeks),we choose to administer ciprofloxacin for a period of seven days followed by furazolidon for seven days to increase patient compliance rates.

MATERIALS AND METHODS

Study population

This prospective double-blinded randomized clinical trial study enrolled 220 patients aged 18-81 years-old with dyspepsia or peptic ulcers who were candidates for endoscopy that referred to Taleghani Hospital in Tehran between April 2007 and February 2008. Exclusion criteria were: (a) age lower than 18 years; (b) use of antibiotics, bismuth salts or nonsteroidal anti-inflammatory drugs and PPI four weeks prior to study entry; (c) previous gastric surgery; (d) severe systemic illnesses such as liver cirrhosis or kidney failure; (d) allergy to any of the antibiotics used in triple therapy or new sequential therapy; and (e) pregnancy.

Written informed consent was obtained from all participants and the study protocol was approved by the Ethics Committees of Shahid Beheshti University of Medical Sciences. At entry, each participant underwent an endoscopy with biopsies for histology and a rapid urease test. Patients were considered *H. pylori*-positive if both tests were positive.

Study protocol

Patients were randomly assigned (110 patients in each group) by a computer generated list to one of the following treatments: i) PPI-based triple therapy that consisted of omeprazole (20 mg), amoxicillin (1 g), and clarithromycin (500 mg) administered twice daily or 2) 14-day new sequential regimen of omeprazole (20 mg), amoxicillin (1 g) and ciprofloxacin (500 mg) twice daily for the first seven days, followed by omeprazole (20 mg), amoxicillin (1 g), and furazoli-

don (200 mg) twice daily for the remaining seven days. Patients were asked to return at the end of the treatment to assess compliance, which was defined as consumption of greater than 80% of the prescribed drugs. Medications were discontinued if any intolerable adverse events such as fever, urticarial rash, or generalized body pain occurred.

Failure of *H. pylori* eradication was evaluated by 13C-urea breath test (UBT) at least four weeks after completion of treatment. UBT was performed with 75 mg of 13C-urea in the fasting state and dissolved in 100 ml of orange juice. The 13C in the expired air was measured 20 minutes later, using an infrared spectrophotometer (IRIS, Dr. Wagner, Bremen, Germany).

Statistical analysis

Results were reported as mean±standard deviation (SD) for quantitative variables and percentages for categorical variables. The groups were compared using the student's t-test for continuous variables and the chi-square or Fisher's exact test if required for categorical variables. *P*- values of 0.05 or less were considered statistically significant. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) for Windows.

RESULTS

A total of 220 patients were enrolled in the study. Upper GI endoscopy was performed for all patients (Table 1). Of total patients, 194 completed their treatments. Patient loss was due to lack of treatment compliance or not performing UBT (Figure 1).

The mean age of patients for PPI-based triple therapy was 45.25±7.59 years, for 14-day new sequential therapy it was 43.70±6.53 years. The male to female

Table 1: Demographic, clinical characteristics and endoscopic findings of patients.*

Variables	New sequential	Standard triple
Male/female	48/46	56/44
Age [mean±SD (years)]	43.70±6.53	45.25±7.59
Smokers n (%)	15 (15.9%)	18 (18%)
History of GI bleeding n (%)	1 (1.06%)	1 (1%)
Endoscopic findings		
GU	9	10
DU	11	16
Gastritis	83	91

*p<0.05 were significant. There were no statistically significant differences between groups in any of the above characteristics.

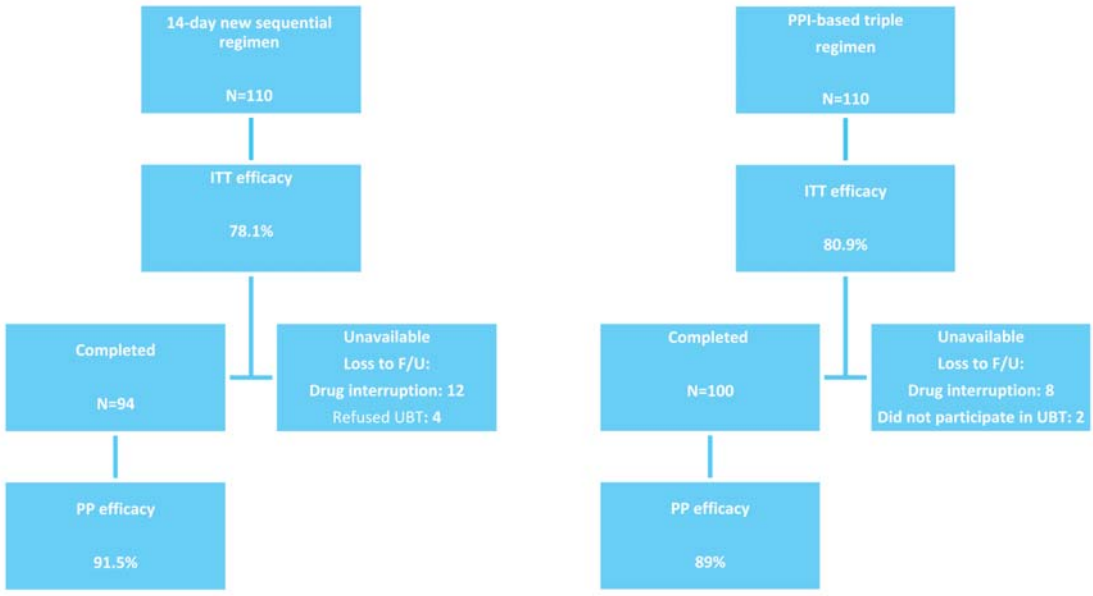

Figure 1: Flow chart of study recruitment and enrollment

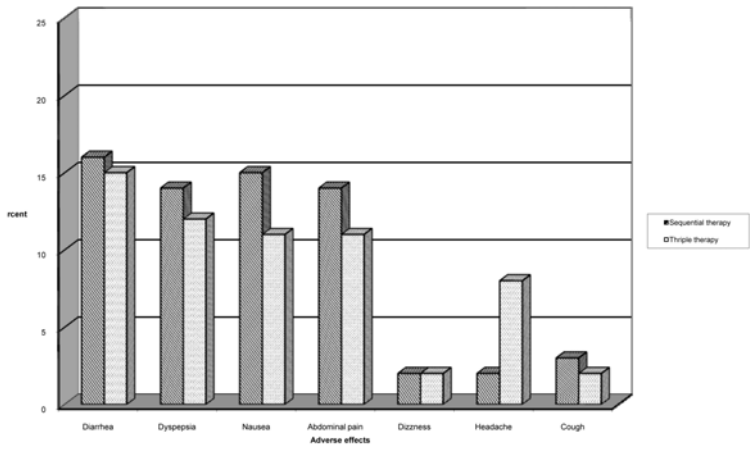

Figure 2: Adverse effects following PPI-based triple and 14-day new sequential therapies.

ratio was 56 to 44 for the PPI-based triple therapy and 48 to 46 for the 14-day new sequential therapy regimens. The two patient groups did not differ in terms of age (p=0.128) and sex (p=0.491).

"Per protocol" eradication rate in the PPI-based standard regimen was 89% whereas in the 14-day new sequential regimen it was 91.5%."Intetion to treat" in the PPI-based standard regimen was 80.9% and in the 14-day new sequential it was 78.1%. No significant difference was noted in eradication rates between the two treatment regimens (p=0.895). A comparison of eradication rates between males and females in the two treatment groups revealed no significant differences between the two genders in each treatment group. In terms of gender, there was no significant difference in eradication rates between men on PPI-based triple therapy and those who received 14-day new sequential treatment (p=0.944). The same was noted for females, in terms of eradication rates between the two treatment regimens (p=0.803).

Common adverse effects are presented in Figure 2. The most common adverse effects in the two groups were diarrhea, dyspepsia, nausea/vomiting and abdominal pain, which were comparable between the two treatment regimens.

DISCUSSION

Despite progress, selection of the best approach for the treatment of *H. pylori* infection remains challenging. Current approaches have emphasized combining two consecutive complementary treatments (sequential therapy), whereas in others, first-line triple therapy followed by a quadruple therapy has been recommended(15).

The present study showed similar eradication rates of *H. pylori* infection between the PPI-based 14-day triple therapy and 14-day new sequential regimen. In this study, we achieved an acceptable eradication rate with both regimens, as evidenced by the 89% eradication rate with the PPI-based triple therapy regimen. This result confirmed acceptable susceptibility of *H. pylori* to clarithromycin in our population, as previously described(16,17).

Antimicrobial drug resistance is a main source for treatment failure and largely responsible for the decline in eradication rates(5).According to recent trials, eradication rates of *H. pylori* infection achieved by first-line triple treatment with a PPI, clarithromycin, and amoxicillin have decreased to 50%-79% worldwide, which is partly due to increasing clarithromycin resistance(18-20). Initially, studies with triple therapy achieved excellent cure rates because of the lower resistance rate to clarithromycin. However, clarithromycin resistance is the cause of eradication failure in one third of patients(8). This resistance is mainly caused by the three point mutations of A2143G, A2142G, and A2142C genes(21). It is also attributable to random point mutations in the 23S ribosome gene of *H pylori*, which prevents binding of the antibiotic to the bacterial ribosome(22). It seems that the 14-day new sequential regimen can not achieve eradication rates superior to clarithromycin-based triple therapy; the two regimens have the same toleration rates in our population. However, the 14-day new sequential therapy may be superior to clarithromycin triple therapy in patients with clarithromycin-resistant *H. pylori* strains(23-26). Of course, the similar eradication rate by the 14-day new sequential and PPI-based triple therapies in our study can be related to a considerable resistance rate to fluroquinolone as reported in some studies in our population(27,28). Fluoroquinolone resistance is rapidly increasing and it has been

suggested that these antibiotics should not be given to patients with prior histories of having received such medications, as resistance is essentially assured(5).

Therapy dose and duration have pivotal roles for providing good cure rates. The success of the PPI plus amoxicillin combination is greatly influenced by treatment duration, such that, in the presence of clarithromycin resistance, a cure rate of approximately 25% is expected after one week of therapy, which increases to 50% with two weeks of treatment(29,30). Although some studies have confirmed similar eradication rates followed by ten-day new sequential and triple therapy regimens(11), other studies found that the ten-day new sequential regimen was significantly more effective than both seven- and ten-day triple regimens(26). In others, a ten-day new sequential therapy was unsuccessful as a therapy for children and young adults who had failed previous treatment regimens(13). Our study showed similar effects of these two regimens in 14-day treatment protocols. In a similar study in Turkey, it was shown that sequential therapy [pantoprazole (40 mg) plus amoxicillin (1000 mg) twice daily for seven days followed by pantoprazole (40 mg), metronidazole (500 mg) and tetracycline (500 mg) twice daily for the remaining seven days] yielded unacceptably low eradication rates of almost 57%; however, there were no significant adverse effects(12). *H. pylori* eradication rate with a standard triple therapy (PPI plus amoxicillin and clarithromycin) for 14 days was also 45% in that study.

However according to our findings, both the PPI-based triple and new sequential therapy for 14 days could similarly lead to acceptable eradication rates of this infection in the Iranian population. Priority of sequential therapy to triple therapy in most previous studies was for the shorter duration of treatment. There are concerns that 7 days of PPI triple-therapy might not be an adequate treatment time; review of the literature has suggested that the optimum duration could be 14 days. Therefore, new sequential therapy should be compared with a 14-day course of PPI-based triple therapy(31,32).

In our study, the observed adverse effects following new sequential therapy were no greater than those experienced with clarithromycin triple therapy. This result was similarly observed in other studies(1,10,11). Adverse effects in the present trial ranged from 2%-16% in both regimens and were mild; no severe adverse effects were observed. In other trials, mild to moderate adverse effects were reported in 21%–48% of patients treated with the triple regimen, whereas no severe adverse effects were observed, such as anaphylaxis reaction to the treatment(33). Some studies have reported mild adverse effects of less than 11% following new sequential protocols and confirmed that the adverse effects were not different from those described with triple therapy(34). It seems that the occurrence of these adverse effects in the two regimens can be dependant on the duration of treatment; however, its range is totally low, especially in our population which had acceptable toleration.

Within the second seven days of treatment, we administered furazolidon instead of clarithromycin because of its similar efficacy, but lower price, lower resistance rate, and greater availability than clarithromycin in Iran(35). We used furazolidon for one week to prevent its more substantial adverse effects, which have been previously described among Iranian patients(36). We studied furazolidon at a dose of 200 mg twice daily because it has been noted that despite less frequent serious adverse effects following the low-dose regimen of this drug, its intent-to-treat eradication rate is not acceptable.

It is noteworthy that the major limitation in this study was the difficulty to obtain cultures due to technical problems.

In conclusion, eradication rates following the PPI-based 14-day triple and 14-day new sequential therapies amongst Iranians are 89.0% and 91.5%, respectively with no significant difference noted between the two treatment schedules. These eradication rates are comparable with obtained eradication rates in other developed countries; however, the rates are higher compared to most developing nations. The frequency of adverse effects following these two regimens is considerably lower than other similar studies and mainly related to mild well-tolerable adverse effects.

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