

Full Length Research paper

Role of fluoroquinolones in two-weeks triple therapy for eradication of *Helicobacter pylori* infection in Iranian population

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Despite reports on high prevalence of *Helicobacter pylori* (*H. pylori*) infection especially in developing countries, considerable low *H. pylori* eradication rate has been shown following different triple therapies. The present study has for the first time assessed and compared the efficacy of the two 14day PPI-based triple therapies with and without a fluoroquinolone among an Iranian population. Two hundred and seventy patients with peptic ulcer and positive *H. pylori* infection were included in the study. Patients were randomly assigned to one of the two treatment protocols. A 14day triple therapy comprising omeprazole 20 mg, amoxicillin 1 g and ofloxacin 400 mg (OAO group) and a 14 day triple regimen comprising omeprazole 20 mg plus amoxicillin 1 g and clarithromycin 500 mg (OAC group) all given twice daily. Cure was defined as a negative urea breath test at least four weeks after the end of treatment. Among 135 patients in each group, 129 patients in OAO group (95.6%) and 100 patients in OAC group (74.1%) could continue treatment protocols and underwent ¹³C-urea breath testing while other ones discontinued because of any intolerable adverse events. The per-protocol eradication rates achieved with OAC regimen was significantly higher than the OAO treatment protocol (89.0 vs 73.6%). Two-week PPI-based triple therapy including amoxicillin and clarithromycin is already an effective regimen for *H. Pylori* eradication while triple therapy comprising ofloxacin is not a recommendable schedule because of high increasing resistance to fluoroquinolones among the Iranian population.

Key words: *Helicobacter pylori*, therapy, resistance, antibiotic.

INTRODUCTION

Association between *Helicobacter Pylori* (*H. Pylori*) infection and some gastrointestinal disorders such as peptic ulcer disease, chronic gastritis, gastric adenocarcinoma and even mucosal-associated lymphoid tissue lymphoma (MALT) has been clearly proven (Paptheodoridis et al., 2006; Farinha and Gascoyne, 2005). It has been also well suggested that *H. Pylori* eradication can effectively lead to cure of peptic ulcer disease. Current choice treatment schedule for eradication of this infection is classical triple therapy including a proton pump inhibitor (PPI) and two antibiotics such as

clarithromycin and either amoxicillin or metronidazole (Katelaris et al., 2002; Gené et al., 2003; Vakil et al., 2004; Cardenas et al., 2006). Furthermore, quadruple therapy including classical triple therapy plus a PPI has been produced for eradicating *H. pylori* infection especially in areas of high prevalence of antibiotic resistance (Gomollón et al., 2000). Despite reports on high prevalence of *H. Pylori* infection among healthy individuals in some developing countries such as Iran, researches on *H. Pylori* eradication indicated considerably low eradication rate following different triple and quadruple therapies generally less than 85% (Everhart, 2000; Nouraie et al., 2009). Therefore, main causes of this low cure rate for preventing *H. Pylori* related disorders should be determined.

Some recent studies should have show an appropriate

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Table 1. Demographic characteristics and clinical data of study patients.

Characteristics	OAO group (n = 135)	OAC group (n = 135)	p-value
Female gender	57 (42.2)	57 (42.2)	---
Age (year)	54.5 ± 10.2	51.5 ± 8.8	0.657
History of GI bleeding	0 (0.0)	1 (0.7)	0.998
History of hospitalization	2 (1.5)	1 (0.7)	0.776
History of Alcohol use	0 (0.0)	1 (0.7)	0.998
History of opium use	5 (3.7)	3 (2.2)	0.723

54.5 ± 10.2 and 51.5 ± 8.8.

consistent cure rate of *H. Pylori* infection following administration of fluoroquinolones plus other antibiotics as triple therapies (Calvet, 2006; Chey et al., 2007). Fluoroquinolones-based triple therapy has recently been studied as second and third line therapy in patients with persistent *H. Pylori* infection. Although its efficacy has been shown, the available clinical trials have involved relatively small numbers of patients and demonstrated variable eradication rates, ranging from 63 to 94% (Chey et al., 2007; Gisbert and Morena, 2006; Gisbert et al., 2006).

The present study for the first time assessed and compared the efficacy of the two 14day PPI-based triple therapies with and without a fluoroquinolone among an Iranian population.

MATERIALS AND METHODS

In a prospective double-blinded randomized clinical trial study, 270 patients (age > 15 years old) with proved peptic ulcer disease or gastritis referred to Taleghani Hospital between April 2007 and February 2008 entered into this study. Positive *H. Pylori* infection was confirmed by using endoscopy with biopsies for histology and a rapid urease test. A biopsy specimen was taken from the antrum and two others from the lesser curvature sites of the antrum and corpus, respectively. The section was fixed and stained with hematoxylin and eosin stain for observing curved rod shaped bacteria on the mucosal surface. Patients' histological findings were blindly evaluated by a histologist. Exclusion criteria were: previous *H. Pylori* eradication therapy, use of antibiotics, bismuth salts or nonsteroidal anti-inflammatory drugs during the previous four weeks, previous gastric surgery, severe systemic illness such as liver cirrhosis or kidney failure, allergy to any of the antibiotics used in classic triple therapies or pregnancy or lactating period.

Positive *H. Pylori* infection was confirmed by using endoscopy with both biopsies for histology and a rapid urease test. Written informed consent was obtained from all participants and the study protocol was approved by the ethics committee of the Shahid Beheshti University of Medical Sciences. Eligible participants were randomly assigned (135 patients in each group) using a computer generated list to one of these treatment protocols: 1) A 14 day triple therapy (OAO group) comprising omeprazole 20 mg, amoxicillin 1 g and ofloxacin 400 mg, all twice daily; 2) A 14day triple regimen (OAC group) comprising omeprazole 20 mg plus amoxicillin 1 g and clarithromycin 500 mg and amoxicillin 1 g, all given twice daily. Both regimens were administered 1 h before breakfast and dinner. Patients were asked to return at the end of the treatment to assess the compliance with therapy that was defined as consumption of greater than 80% of the prescribed drugs. Failure of *H. pylori*

eradication was mainly evaluated by using a ¹³C-urea breath test (UBT) using an infrared spectrophotometer (IRIS, Dr. Wagner, Bremen, Germany) at least four weeks after completion of the treatment.

Statistical analysis was performed with Chi-square test and p value ≤ 0.05 was considered statistically significant. Analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age of patients in the OAC and OAO group was 54.5 ± 10.2 and 51.5 ± 8.8 years, (Table 1) respectively with the male to female ratio of 2.4 in both groups. The two study groups were matched for sex and age. Among 135 patients in each group, 129 patients in OAO group (95.6%) and 100 patients in OAC group (74.1%) could continue treatment protocols and underwent ¹³C-urea breath testing while the others discontinued because of any intolerable adverse events such as fever, urticarial rash, or generalized body pain. The per-protocol eradication rates, achieved with OAC regimen, was significantly higher than the OAO treatment protocol (89.0 vs. 73.6%, p = 0.0036).

There were no major side effects that interrupted treatment in either group. Three patients from the OAO group complained of minor side effects as mouth burning in two patients and diarrhea in one of them, whereas undesired effects were reported in 2 of 100 patients in the OAC group, including diarrhea. All side effects disappeared spontaneously after stopping the study medication. The proportions of minor side effects experienced were significantly similar in the two treatment groups.

DISCUSSION

The present study tried to confirm the efficacy of PPI-based triple therapies and also assessed the beneficial effects of fluoroquinolones administration as a component of these triple treatment protocols, We could show with high *H. Pylori* eradication rate following a 2 week triple therapy including omeprazole plus amoxicillin and clarithromycin among the Iranian population. The efficacy of omeprazole/amoxicillin administration for *H. Pylori*

eradication in reported researches was different and eradication rates ranged from 0 to 90% (Zala et al., 1994). Most researches suggested that omeprazole-based triple therapy with clarithromycin and amoxicillin was the best regimen for the treatment of patient with *H. Pylori* positive ulcer disease with regard to safety, pain relief and ulcer healing either for a 1 or 2 weeks regimen (Labenz et al., 1993; Gisbert et al., 1998). However, some studies showed notable decline in eradication rates and high failure rate of this triple-drug regimen in nearly one quarter of all patients (Saad and Chey, 2006; Fuccio et al., 2007). Our findings showed that the susceptibility to PPI and clarithromycin might be acceptable for eradicating and preventing *H. Pylori* infection, whereas it is believed that the widespread use of these antibiotics led to the dramatic increase of failure rate due to high drug resistance. According to some 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% globally in part due to increasing clarithromycin resistance (Graham et al., 2007; Malfertheiner et al., 2007; Vakil and Megraud, 2007) and the initial studies with triple therapy achieved excellent cure rates, because of lower resistance rate to clarithromycin.

Similarly to our study, Minakari et al. (2010) in a similar randomized controlled trial among the same study population revealed acceptable efficacy and safety of quadruple treatment schedule including a fluoroquinolone for *H. Pylori* eradicating. Although eradication rate and overall prevalence of minor side effects were in comparable with our finding, but found eradication rates in both studies were partially low (Minakari et al., 2010). This notable low eradication rate following triple therapy comprising fluoroquinolones may be due to increasing of *H. Pylori* resistance against these antibiotics in our population. Resistance to fluoroquinolones has been also increasing in other populations and it has been suggested that the resistance is most likely mediated through point mutation in *gyrA* encoding a subunit of DNA gyrase (Mogg et al., 2005; Chatsuwan and Amyes, 1999; Bogaerts, 2006). However, it was also indicated that the resistance rates against fluoroquinolones varied following administration of different types of these strains. Kumala et al. showed that the ciprofloxacin resistance rate was higher than other types of fluoroquinolones such as ofloxacin, sparfloxacin, gatifloxacin, levofloxacin and moxifloxacin (Kumala and Rani, 2006). A reason for this high resistance may be that some types of this antibiotic subgroup is frequently used more for treating infections which were originated from multiple organs such as urinary tract and respiratory infections.

Finally, it can be concluded that the 14 day PPI-based triple therapy including amoxicillin and clarithromycin is already an effective regimen for *H. Pylori* eradication while triple therapy comprising ofloxacin is not a recommendable schedule because of high increasing resistance to fluoroquinolones among the Iranian

population.

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