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ORIGINAL ARTICLE

Comparing furazolidone and tetracycline in quadruple therapy for eradication helicobacter pylori in dyspepsia patients

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ABSTRACT

Aim: To comparing furazolidone and tetracycline in quadruple therapy for eradication of helicobacter pylori in dyspepsia patients.

Background: Helicobacter pylori eradication is the main step in dyspepsia and peptic ulcer management. In Iran different regimens have been proposed, however, most of our patients are resistant to metronidazole. In the current study we compared furazolidone- and tetracycline-based quadruple therapy for eradication of H.pylori in a group of Iranian patients with dyspepsia.

Patients and methods: Dyspeptic patients were randomly assigned in 2 groups and received omeprazole 20mg/twice a day, bismuth subcitrate 200mg/q6h, amoxicillin 1000mg/twice a day in association with furazolidone 100mg/ twice a day (OAB-F regimen) or tetracycline 500mg/ twice a day (OAB-T regimen). Stool antigen test was used to detect H. pylori eradication.

Results: Totally, 100 patients completed the desired regimen including 49 in OAB-F and 51 in OAB-T regimen. Following the first week, H. pylori was eradicated in 97.9% of OAB-F and 96% of OAB-T subjects, however, the difference did not reach a statistical significant level. These figures were 85.7% and 80.4% following the 4th week, respectively (NS).

Conclusion: Both furazolidone-and tetracycline-based quadruple therapy were revealed to be effective for eradication of H.pylori, however, furazolidone is suggested for population resistant to metronidazole since it is cheaper and more available.

Keywords: *Furazolidone, Tetracycline, Helicobacter pylori, Eradication, Dyspepsia*.

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INTRODUCTION

Helicobacter pylori (H. pylori) infection is by far the most common chronic bacterial infection among humans (1). In developing countries, it is more frequent and occurs earlier (1). Approximately, 80% of adults residing in developing countries are affected (1,2). Chronic gastritis is usually detected during endoscopy, however, H. pylori infection is strongly associated with peptic ulcer, adenocarcinoma of stomach and gastric MALToma (3-8). Therefore, prompt diagnosis and appropriate management is of utmost importance.

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H. pylori infection is diagnosed by either invasive (endoscopy and biopsy) or non-invasive (urease breath test (UBT), serology, and stool antigen testing) techniques. Nevertheless, non-invasive techniques including serology and stool antigen are usually applied for early diagnosis while UBT is used for eradication follow up (9,10).

Various regimens have been proposed for H. pylori eradication, among which triple therapy with a proton pump inhibitor (PPI)(i.e., omeprazole) in combination with amoxicillin and clarithromycin or quadruple therapy with a pump inhibitor, bismuth, metronidazole and tetracycline are more commonly appreciated. However, proposed regimens have limitations including expenses, availability, drug side effects, patient's tolerance, and microorganism resistance, thus, investigations are still continuing to find more tolerable appropriate regimens. Furazolidone has been studied in scanty researches (11-17), however, with respect to H. pylori resistance to metronidazole among Iranian patients (18-20) and availability of furazolidone, the present study was conducted to compare furazolidone and tetracycline in quadruple therapy for eradication of H. pylori in Iranian dyspepsia patients.

PATIENTS and METHODS

This double-blinded randomized clinical trial was conducted during a 6-month period in Khatam hospital in Zahedan. Patients with gastrointestinal manifestations including heart burn, flatulence, and post-prandial nausea were visited by an expert gastroenterologist. The following exclusion criteria were applied at baseline: age >50 years, weight loss >10% during the past 6 months, severe anorexia, dysphagia, odynophagia, anemia, jaundice, abdominal mass, lymphadenopathy, family history of gastric or esophageal cancer, past history of gastric surgery, recurrent vomiting, hematemesis, prior history of H. pylori treatment, antibiotic treatment during the 4 weeks prior to the study or treatment with pump inhibitors during the week before the study.

Included patients were those who were positive for both serum IgG against H. pylori (Serum Anti-H.Pylori IgG, DIAPLUS, Germany) and stool antigen (ASTRA, Italy). Then, patients were randomly assigned in either group A or B. Group A (OAB-F) received omeprazole (20 mg/bid), bismuth subcitrate (200mg/qid), amoxicillin (1000mg/bid) and furazolidone (100mg/bid) for 14 days. Group B (OAB-T) received omeprazole (20 mg/bid), bismuth subcitrate (200mg/qid), amoxicillin (500mg/bid) and tetracycline (500mg/bid) for 14 days. Patients were explained about the protocol and probable side effects. In case of severe side effect, the patient was excluded. Patients were visited at weeks 1 and 4 and finally after the regimen completion, while stool antigen testing was applied. All tests were achieved by a single laboratory staff and an expert pathologist who was blind to the study group managed the protocol.

All patients were requested to complete an informed consent. A checklist of demographic, laboratory, and pathologic features was completed prior to the commencement of therapy and during follow up. Data were analyzed by SPSS for Windows (version 10.5, USA).

RESULTS

Totally, 109 patients were enrolled, of whom 9 were excluded. Fortunately, none of the subjects developed life threatening side effects, however, minor tolerable complications including, pruritus, nausea, and vomiting occurred. Finally, 49 patients (26 males and 23 females) in group A versus 51 patients (32 males and 19 females) in group B completed the desired regimen. The mean age of the patients was 28.7±6.3 and 28.3±6.3 years in group A and B, respectively.

After the first week, response to therapy was 97.9% and 96% in group A and B, respectively,

however, these figures were 85.7% and 80.4% after the 4th week, respectively (table 1). Despite the differences in the aforementioned frequencies, none reach the statistical significant level.

Table 1. *Response to therapy based on stool antigen negativity after 1 and 4 weeks of therapy*

	No. of patients	Negativity of stool antigen after the 1st week	Negativity of stool antigen after the 4th week
OAB-F	49	48(97.9%)	42(85.7%)
OAB-T	51	49(96.0%)	41(80.4%)

OAB-F: Omeprazole/Amoxicillin/Bismuth/Furazolidone
OAB-T: Omeprazole/Amoxicillin/Bismuth/Tetracycline

DISCUSSION

Studies conducted in developing countries demonstrated the increasing frequency of H. pylori infection while they showed the necessity for microorganism eradication through a cheap, tolerable and effective regimen (11).

Our studied population had functional dyspepsia and underwent noninvasive diagnostic approach for early diagnosis of H. pylori infection, while diagnostic endoscopy was not advised based on age of <50 years and lack of alerting symptoms (21). Serum IgG anti H.pylori is a cheap suitable approach for early diagnosis of H. pylori. In a metanalysis, sensitivity and specificity of IgG anti H.pylori-ELISA kit was 85% and 79%, respectively (22). Meanwhile, Stevens et al have reported an accuracy of 78% for anti H.Pylori ELISA kit in 558 samples (23). Nevertheless, diagnostic value of serology approaches depends mainly on H.Pylori prevalence and the underlying etiology (dyspepsia, peptic ulcer, etc.). However, stool antigen testing and urease breath test (UBT) are preferable to serology for early diagnosis and follow up (24-26). Therefore, we used serology and stool antigen testing for early diagnosis and stool antigen testing for follow up. Vaira et al reported stool antigen test to have sensitivity and specificity of 94% and 86%, respectively (25,26). These figures were 94% and 92% in Trevisani et al study (27). On the other hand, stool antigen testing was showed to be a valuable test for eradication follow up, however, the exact timing is a matter of controversy. Some investigators have proposed the 4th week after the therapy to be a suitable point (25-28) while Vaira et al reported a positive predictive value (PPV) of 100% and a negative predictive value (NPV) of 91% if the test had been offered 1 week following the therapy (26). We advised our subjects to perform the test at weeks 1 and 4.

Antibiotics, bismuth and PPIs may be associated with false negative stool antigen testing results (29), however, Makristathis et al reported 32% false positive results among 41 patients after the 5th week (30).

Prior investigators have proposed different eradication regimens. Suitable regimens may be advised based on the following criteria: expenses, side effects, availability, easy to use, and drug resistance pattern. A combination of omeprazole, bismuth, metronidazole and tetracycline is usually prescribed, however, combination of a PPI, clarithromycin, amoxicillin, and metronidazole is quite common in USA. Resistance to metronidazole is becoming a worldwide health concern. In a well designed study in USA, resistance was reported 22-39% (31), however, in another study 36.9% of strains were resistant to metronidazole (32). In Iran, Safaralizadeh et al showed 33% of H. Pylori specimens to be metronidazole-resistant (33). Unfortunately, scanty reports have addressed furazolidone as an alternative. Some studies have suggested furazolidone as a second choice of treatment (34). Malekzadeh et al compared furazolidone versus metronidazole in quadruple therapy for eradication of H. pylori in duodenal ulcer disease. After the 4th week, 75% of patients became H.pylori-free in furazolidone-based regimen in comparison with 55% of metronidazole-based regimen ($p<0.05$)(35).

Furthermore, Fakheri et al compared clarithromycin vs. furazolidone in quadruple therapy regimens for the treatment of H.pylori in a population with a high metronidazole resistance rate and reported an eradication rate of 85% and 84%, respectively (36). In another study, they compared the following 3 regimens: (A): omeprazole-amoxicillin-furazolidone (100mg/bid), (B): omeprazole-amoxicillin-bismuth-furazolidone (100mg/bid), and (C): omeprazole-amoxicillin-bismuth-furazolidone (200mg/bid) and reported 54%, 72%, and 92% eradication rate, respectively (37). Therefore, furazolidone with a higher dose (200mg/bid) is more effective, however, we have found an eradication rate of 85% with 100mg/bid. On the other hand, Daghaghzadeh et al have compared one-week versus two-week furazolidone-based quadruple therapy as the first-line treatment for Helicobacter pylori infection and reported an eradication rate of 84.8% and 82.6%, respectively (17). In Buzas study furazolidone-based regimen with PPI revealed an eradication rate of 76.3%, whereas, furazolidone-based quadruple therapy had eradicated H.Pylori in 83.4% of cases (24).

In conclusion, a quadruple regimen of amoxicillin, bismuth, omeprazole and furazolidone is a quite tolerable, cheap and available therapeutic approach for H. pylori eradication among Iranian patients.

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