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ORIGINAL ARTICLE

Comparison of two different eradication regimens for H. pylori: amoxicillin, metronidazole, bismuth and omeprazole (OMAB) versus the new regimen of penbactam, clarithromycin and omeprazole (OPC); a randomized clinical trial

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ABSTRACT

Aim: The present study aimed to compare the eradication rate of H. pylori by traditional amoxicillin, metronidazole, bismuth, and omeprazole regimen, with a new one using clarithromycin, omeprazole and ampicillin/sulbactam (penbactam).

Background: Due to the appearance of Amoxicillin-resistant H. pylori strains all over the world, the decreased efficacy of conventional Amoxicillin-containing treatment regimens has become a matter of concern.

Patients and methods: A total of 332 dyspeptic patients whose H. pylori infection was confirmed by endoscopy and rapid urease test (RUT) were randomized into two groups: group A, comprising 162 patients who received the traditional quadruple treatment regimen for H. pylori (bismuth 240 mg, omeprazole 20 mg, amoxicillin 1gr, and metronidazole 500 mg twice daily) and group B, containing 170 patients who received clarithromycin 500mg, penbactam (ampicillin 250 mg plus sulbactam 175 mg) and omeprazole 20 mg twice daily. Both groups were given the treatment for 2 weeks, and both underwent UBT 4 weeks after the end of treatment; UBT negative patients were considered responders and the rate of treatment response was compared by per-protocol and intention-to-treat analysis between two groups.

Results: The eradication rate was 56.4% in group A and 87%in group B by per protocol analysis. The eradication rates were 48.8% and 81.7% according to intention-to-treat analysis in groups A and B respectively. The eradication rate was higher in group B patients taking penbactam, omeprazole and clarithromycin (P<0.0001).

Conclusion: Our study showed that using ampicillin/sulbactam instead of amoxicillin, clarithromycin and omeprazole increased the eradication rate of H. pylori significantly.

Keywords: Dyspepsia, RUT, UBT, H. pylori.

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INTRODUCTION

Triple therapy of bismuth salts combined with two antibiotics was first used by Borody et al. (1). In 1988, they published the results of 100 patients treated with triple therapy with bismuth and amoxicillin for 4 weeks and metronidazole for the first 2 weeks, achieving a cure rate of 94%. In 1994, at the NIH Consensus Conference on H. pylori, the bismuth-based triple therapy was one of the most widely recommended regimens (2).

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At present, triple therapy regimens with PPI, clarithromycin, and amoxicillin or metronidazole are considered to be the most effective combinations for the treatment of H. pylori infection. Because of their safety, cost effectiveness and simplicity, these PPI-based triple therapies are the most frequently used treatments worldwide (3,4). The two most widely used triple regimens include a combination of a PPI, clarithromycin and amoxicillin and a combination of a PPI, clarithromycin and metronidazole. It has not been clearly established whether one regimen is superior to the other. The third Maastricht Consensus Conference reported that the urea breath test, stool antigen tests, and serological kits are highly accurate and non-invasive tests that should be used for the diagnosis of H pylori infection. Triple therapy using a PPI with clarithromycin and amoxicillin or metronidazole taken twice daily remains the recommended first choice treatment. Bismuth-containing quadruple therapy, if available, is also a first line treatment option. Moreover, rescue treatment should be based on antimicrobial susceptibility (5). Bismuth-based triple therapy (the first used) and PPI-based triple therapies (combined with two antibiotics, including amoxicillin, metronidazole, or clarithromycin) have been the most widely recommended H.pylori treatment regimens. PPI-based regimens are superior to H2-antagonist-based ones. Among the factors influencing the efficacy of therapy, resistance to clarithromycin and metronidazole are the most important risk factors for eradication failure. Antibiotic resistance is the main source of failure of H. pylori eradication, and beta-lactamase production by resistant H. pylori strains is another possible mechanism underlying ineffectiveness of an amoxicillin-based triple or quadruple therapy (6). In addition, antibacterial activity of beta-lactamase inhibitor agents such as clavulanic acid and sulbactam has been demonstrated in a number of in vitro studies (7,8). So, it is possible that combination of amoxicillin or ampicillin with betalactamases (e.g. clavulanate or sulbactam) could increase H.pylori eradication rate. The aim of our study was to compare the eradication rate of traditional quadruple therapy for H.pylori comprising omeprazole, bismuth, amoxicillin and metronidazole with new regimen of clarithromycin, omeprazole and ampicillin/sulbactam in Iranian patients.

PATIENTS and METHODS

In the present randomized clinical trial, 332 patients whose H. pylori infection was confirmed by upper endoscopy and rapid urease test (UBT) were randomly assigned to two different H. pylori eradication treatment groups. Group A (162 patients) received traditional regimen for H.pylori eradication as follows: amoxicillin 1gr, metronidazole 500 mg, bismuth 240 mg and omeprazole 20 mg twice daily. 22 patients were excluded from per protocol population due to non-compliance and minor side effects. In group B (170 patients), 10 patients were excluded from per protocol population for the same reasons. Patients on this group received clarithromycin 500 mg, penbactam (ampicillin 250 mg plus sulbactam 175 mg) and omeprazole 20 mg twice daily. Patients in both groups received treatment for 2 weeks. UBT was done 4 weeks after the end of therapy in both patient groups. UBT negative patients were considered responders and the percentage of UBT negative patients in both groups were compared by per-protocol and intention-to-treat analysis. The results were compared by using Chi-Square analysis.

We considered ethical aspects of our study by taking informed consent from our patients.

RESULTS

The patients in group A (n=162) and group B (n=170) were compared according to response to

Table 1. Comparison of the eradication rate of H. pylori in two treatment groups

Treatment regimen	Total number of patients	Number of patients per-protocol	Treatment response	Eradication rate PP‡	Eradication rate ITT§
OMAB*	162	140	79	56.4%	48.8%
OPC†	170	160	139	87%	81.7%

* Omeprazole, Metronidazole, Amoxicillin, Bismuth
† Omeprazole, Penbactam, Clarithromycin
‡ Per-protocol analysis
§ Intention to treat analysis

therapy. The male to female ratio was 1.2 and 1.4 in groups A and B respectively.

The results of per-protocol and intention-to-treat populations were compared using Chi-Square analysis. There was a better eradication rate or response in group B taking OPC regimen with a statistically significant difference on both per protocol ($p<0.001$) and ITT ($P<0.0001$) analysis (Table 1).

DISCUSSION

Despite the extensive body of research over the last 25 years, the treatment of H. pylori remains a challenging clinical problem. The increasing antimicrobial resistance and the decreasing eradication rates are the results of the widespread use of antibiotics. The third Maastricht Consensus Report agreed that effective treatment for H. pylori should achieve an intention-to-treat (ITT) eradication rate of over 80% (5). However, in clinical practice eradication rates are lower than 80% for many of the standard treatment regimens. A number of factors such as duration of treatment, choice of antibiotics, new drug combinations, improvement of patient compliance and novel agents may help to improve the eradication rates.

Pre-treatment antibiotic resistance is the most important factor in non-responsiveness to initial treatment. To define the effect of pre-treatment H. pylori resistance to metronidazole or to clarithromycin on the success of antimicrobial therapy, Dore (9) conducted a meta-analysis and identified 49 papers with 65 arms for metronidazole. Metronidazole resistance reduced the effectiveness by an average of 38%. Susceptibility tests for clarithromycin were performed in 12 studies (501 patients), and resistance to this drug reduced effectiveness by an average of 55%. Another meta-analysis evaluated the influence of in vitro metronidazole resistance on the efficacy of metronidazole containing anti-H. pylori regimens (10). A total of 91 treatment arms, including 4823 patients, were evaluated. Eradication rates were 90% in susceptible strains, but 75% in resistant ones. The negative effect of metronidazole resistance has been confirmed in a more recent meta-analysis (11), which has concluded that metronidazole or clarithromycin pre-treatment resistance is the main factor responsible for treatment failure with regimens that use these compounds, emphasizing the fact that more effective treatments are needed for places where drug resistance is common. Mehrdad et al. showed that quadruple therapy consisting of sultamicillin 2 x 375 mg/d instead of amoxicillin was as effective as the standard amoxicillin-based quadruple therapy and was well tolerated by all patients (12). Amoxicillin is the only β-lactam used to treat H. pylori infection and it is included in most of current therapeutic regimens. Until recently, resistance to amoxicillin was considered to be absent, or very rare; however, amoxicillin-resistant H. pylori strains have now been identified in different countries (13,14). The world-wide prevalence of resistance to amoxicillin is 0-41% (15). In the two previous studies in Iran,

investigators reported 7 and 27% amoxicillin resistance among H. pylori isolates (16).

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