A Randomized Clinical Trial Comparing the Efficacy and Tolerability of Two Quadruple Regimens: Bismuth, Omeprazole, Metronidazole with Amoxicillin or Tetracycline as First-Line Treatment for Eradication of Helicobacter Pylori in Patients with Duodenal Ulce

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Abstract

Aim: To evaluate the efficacy and tolerability of replacing tetracycline with high dose of amoxicillin in bismuth-based quadruple therapy for H.pylori eradication.

Methods: This randomized, open label clinical trial study was performed on 228 patients with H.pylori infection and duodenal ulcer without the history of previous H.pylori treatment. Patients were randomly divided into two groups. Group one received metronidazole 500mg, bismuth subcitrate 240mg and amoxicillin 1000mg, all three times a day and omeprazole 20 mg twice a day (amoxicillin group)for14 days. The second group received metronidazole 500mg three times a day and bismuth subcitrate240mg and tetracycline HCL 500mg both four times a day and omeprazole 20 mg twice a day (tetracycline group), for 14 days. Evaluation for compliance and drugs side effects were done after two weeks. Eight weeks after treatment, H.pylori eradication rate was assessed by c13-urease breath test.

Results: Two hundred twenty-eight patients were enrolled. There was no statistically significant demographic difference between two groups. Amoxicillin containing regimen achieved higher Eradication rate: 105 of 110 ,95.51% (95%CI 91.5% to 99.3%) and 88 of 105, 83.8% (95% CI 76.7% to 90.8%) by per-protocol analysis (p-value=0.005) and 92.9%(95%CI 88.1% to 97.6%) and 76.5% (95% CI 68.7% to 84.2%) by intention-to-treat (p-value=0.001) for amoxicillin and tetracycline groups, respectively. Adverse events were statistically more significant higher in Tetracycline group (65.2%) amoxicillin group (43.4%) (P value = 0.001).

Conclusion: Bismuth based quadruple therapy included high dose of amoxicillin and metronidazole has an acceptable H. pylori infection eradication rate with good tolerance in patients with duodenal ulcer. This can overcome treatment resistance in areas with high prevalence of metronidazole and clarithromycin resistance

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Protocol

introduction

Step 1.
Helicobacter pylori(H. pylori) is a gram-negative bacterium that infects approximately 50% of people in industrialized nations and up to 80% in less-developed countries (1). H. pylori causes peptic ulcer disease, chronic gastritis, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma (2). Although the bacterium is susceptible to most antimicrobial agents invitro, successful treatment of H.pylori remains a challenge (3). Factors contributing to success in H. pylori treatment are drug efficacy, host compliance, and bacterial resistance (1, 2). Resistance to commonly used drugs such as metronidazole and clarithromycin, is the most important reason for treatment failure of current regimens (1). Emerging evidence shows high resistance to clarithromycin in countries with high consumption of macrolide derivatives (4), whereas regimen containing clarithromycin was reported to achieve 80% eradication rate (5). Previous studies from our region (Iran) revealed that more than 20% of H. pylori isolates were resistant to clarithromycin and that over 50% of the H. pylori isolates were resistant to metronidazole (6-8).
Due to high resistance to metronidazole and clarithromycin, regimens containing these antibiotics are not efficient (9). In some studies on patients with metronidazole- and clarithromycin-resistant H. pylori, bismuth-based quadruple therapy was reported as a preferable regimen for eradication of H. pylori (10, 11). This bismuth-based quadruple therapy includes bismuth, a proton pump inhibitor (PPI), and tetracycline together with metronidazole or tinidazole, with proper doses and duration. Quadruple regimen with suboptimal metronidazole doses (<1500 mg/day) was reported to achieve an overall eradication rate of 70% (3,4). Increasing the dose of metronidazole in bismuth-based quadruple therapy was the first step in increasing eradication rates to acceptable levels, and bismuth compound was reported to be necessary for such response (12, 13). However, low compliance, as well as increased side effects, are major issues that arise if full-dose metronidazole and tetracycline are used. There is also some evidence suggesting an increase in H.pylori resistance to tetracycline (14-16).
Outcomes with substitution of tetracycline with amoxicillin in bismuth-based quadruple therapy have not been widely studied, especially in countries with high H.pylori resistance to metronidazole and clarithromycin such as Iran. Our pilot study revealed that a very good H.pylori eradication rate could be achieved with a modified bismuth-based quadruple therapy containing high-dose amoxicillin (3 g/day), adequate-dose metronidazole (1.5 g/day), and a PPI. Therefore, this open-label, randomized clinical trial was designed to compare the classic bismuth-based quadruple regimen containing metronidazole (1500mg/day) with a modified bismuth-based quadruple therapy containing high-dose amoxicillin (3 g/day), metronidazole (1.5 g/day), and a PPI, with the aim to compare eradication rates, adverse effects, and patient compliance

Trial setup

Step 2.
Time frame:
The trial was started at October20, 2014
The trial was ended at July15, 2016

Trial location:
Division of Gastroenterology, Department of Internal Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Study design:
prospective, randomized, open-label clinical trial

patient population

Step 3.

Inclusion criteria:

Criteria for inclusion in this study were as follows:
no history of treatment for *H.pylori* eradication, age above 18 years, endoscopically confirmed diagnosis of duodenal ulcer, and positive rapid urease test.

Exclusion criteria:

Patients with a history of previous gastric surgery, allergy to antibiotics, those who were treated with antibiotics in the preceding eight weeks, those with major systemic disease, and those who were pregnant or lactating were excluded from the study.

End points

Step 4.

The primary endpoint was *H. pylori* eradication rate by intention-to-treat (ITT) analysis.

The secondary endpoint was frequency of adverse effects and treatment compliance

Interventions

Step 5.

After the patients provided consent to participate in this trial, they were randomly assigned at a 1:1 ratio to receive one of the following two treatment regimens.

The amoxicillin group (group I) received metronidazole 500mg, amoxicillin 1000mg, bismuth subcitrate 240mg, all three times a day, plus omeprazole 20mg twice a day, for 14 days.

The tetracycline group (group II) received omeprazole 20mg twice a day; bismuth 240 mg, and tetracycline HCl 500 mg, both four times a day;and metronidazole 500 mg three times a day, for 14 days. Omeprazole and bismuth were taken before meals, and antibiotics were used after meals.

All patients were instructed on potential adverse effects and kept under observation during treatment for evaluation of adverse effects and compliance. All patients were requested to record any adverse effects that occurred during therapy, including bad taste, diarrhea, dizziness, weakness, nausea, loss of appetite, vomiting, fatigue, fever, and skin rash.

Severe adverse effects were defined as those that would be considered to disrupt daily activities that required treatment discontinuation by the patient.

outcomes

Step 6.

For evaluation for the primary outcome of *H. pylori* eradication rate, patients were asked to stop the PPI or the H2 blocker for at least four weeks before follow-up evaluation.

Eight weeks after conclusion of the two-week study treatment, patients were assessed by the C13urease breath test by personnel who were blinded to the treatment, and a value of less than 4% was defined as successful *H. pylori* eradication.

For evaluation of secondary outcomes, data on adverse effects were collected through a standard sideeffect questionnaire, and good compliance was defined as ingesting more than 80% of the total number of doses included in the regimen.

Sampling and blinding

Step 7.
Sample size for the trial was calculated based on the following assumptions. By ITT analysis, average rate of successfully achieved eradication of *H.pylori*with the standard quadruple therapy was 80% .

Based onour pilot study results showing an *H.pylori* eradication rate of 94% with the modified bismuth-based quadruple therapy containing high-dose amoxicillin (3 g/day),adequate-dose metronidazole dose (1.5 g/day) and omeprazole, we chose delta of 14%, a two-sided alpha value of 0.05, and a power of 80%.

based on these assumptions at least 208 participate (104 subjects in each group) would be required. n order to accommodate a 10% rate of lost to follow-up, we enrolled 228 patients.

Statistical methods

Step 8.
All registered data were analyzed using SPSS software version 22 for Windows (SPSS, Chicago, IL). Data were presented as means with standard deviation (SD), frequencies, and percentages.

The chi-square and Fisher's exact tests were used for comparison of categorical data between the two groups. *P* values of less than 0.05 were considered significant for all analyses.

ITT and per-protocol analyses were performed to calculate eradication rates. The ITT analysis included all randomized patients. Individuals who did not take at least 80% of the drugs andthose with unknown post-treatment *H. pylori* status were excluded from the PP analysis. Odds ratios with 95% confidence intervals (CIs) were calculated where appropriate

Ethical Consideration

Step 9.
This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences in Yazd, Iran and registered with the protocol number Ir.ssu.rec.1394.13712" on september 20, 2014. Participants provided written informed consent and were included in the study after they were provided information on treatment methods.
This trial was also registered with Thai Clinical Trial Registry (Number: TCTR20170623004).

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