

RESEARCH ARTICLE

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 Ulcer: A Randomized Clinical Trial

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Abstract

Aim

To evaluate the efficacy and tolerability of tetracycline vs. high-dose amoxicillin in bismuth-based quadruple therapy for *Helicobacter pylori* (*H. pylori*) eradication.

Methods

This randomized, open-label clinical trial included 228 patients with *H. pylori* infection and duodenal ulcer without a history of *H. pylori* treatment. Patients were randomly divided into two groups. The amoxicillin group received metronidazole 500mg, bismuth subcitrate 240mg, and amoxicillin 1000mg, all three times a day, plus omeprazole 20 mg twice a day, for 14 days. The tetracycline group received metronidazole 500mg three times a day; bismuth subcitrate 240mg and tetracycline HCl 500mg, both four times a day; and omeprazole 20 mg twice a day, for 14 days. Evaluation for compliance and drug-related adverse effects were evaluated at the end of two weeks. Eight weeks after the end of treatment, the rate of *H. pylori* eradication was assessed by the C¹³ urease breath test.

Results

There were no significant demographic differences between the two groups. Eradication rate was higher with the amoxicillin-containing regimen than the tetracycline-containing regimen: 105/110 (95.51%; 95% confidence interval, 91.5%–99.3%) vs. 88/105 (83.8%; 95% CI, 76.7%–90.8%) by per-protocol analysis ($p = 0.005$) and 92.9% (95%CI, 88.1%–97.6%) vs. 76.5% (95%CI, 68.7%–84.2%) by intention-to-treat analysis (ITT, $p = 0.001$). Adverse

effects were significant higher in the tetracycline group than in the amoxicillin group (65.2% vs. 43.4%; $p = 0.001$).

Conclusion

Bismuth-based quadruple therapy including high-dose amoxicillin and metronidazole achieved an acceptable rate of *H. pylori* infection eradication with good tolerance in patients with duodenal ulcer. This regimen can overcome treatment resistance in areas with high prevalence of metronidazole and clarithromycin resistance.

Trial registration

The Thai Clinical Trial Registry (TCTR) [20170623004](https://www.clinicaltrials.gov/ct2/show/study/20170623004)

Introduction

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 *in vitro*, 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 regimens 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.

Materials and methods

Patient population

This was a prospective, randomized, open-label clinical trial study conducted at ShahidSa-doughi University (SSU) of Medical Center, a tertiary care hospital located in Yazd, Iran. 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 rapidureasetest. 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. 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.

Registration

Ethics approval for this study was obtained from Yazd University Medical Sciences ethics committee on September 20, 2014, prior to patient enrollment. The clinical trial registration was completed retrospectively several months after patient enrollment was started, due to a miscommunication with the institution. We emphasize that our study begins and progress with complete consideration of ethical rules. The authors confirm that all ongoing and related trials related to this study are registered.

Intervention

Patients were enrolled between October 20, 2014 and July 15, 2016. 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

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 C¹³ urease 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 side effect questionnaire, and good compliance was defined as ingesting more than 80% of the total number of doses included in the regimen.

Sampling and blinding

Sample size for the trial was calculated based on the following assumptions. Average rate of successfully achieved eradication of *H.pylori* with the standard quadruple therapy was 80% [17]. Based on our 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 a two-sided alpha value of 0.05, and a power of 80%. Based on these assumptions at least 208 participants (104 subjects in each group) would be required. In order to accommodate a 10% rate of lost to follow-up, we enrolled 228 patients.

Statistical methods

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 (PP) 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 and those 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

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). The Consort 2010 checklist, the study protocol and the Ethic approval of study are given [S1 Checklist](#), [S1 File](#) and [S2 File](#).

<http://dx.doi.org/10.17504/protocols.io.mdjc24n>

Results

Patient characteristics and compliance

A total of 228 patients who were eligible were recruited from the SSU Gastroenterology Department. There were no significant differences in baseline characteristics including age and sex between the two treatment groups (Table 1). All patients except those who were lost to follow-up and those who could not tolerate the regimen were assessed by the C¹³ urease breath test after the conclusion of treatments. The CONSORT flow diagram is depicted in Fig 1.

H. pylori eradication rates

Overall, the eradication rate by per-protocol analysis was 105/110 (95.51%; 95%CI, 91.5%–99.3%) in group I and 88/105 (83.8%; 95%CI, 76.7%–90.8%) in group II, which was significantly different between the two treatment groups (*p* = 0.005). As presented in Table 2, the ITT analysis also revealed that the eradication rates were significantly different between the amoxicillin and tetracycline groups (92.9%; 95%CI, 88.1%–97.6% and 76.5%; 95%CI, 68.7%–84.2%, respectively; *p* < 0.001). These results clearly showed that the *H. pylori* eradication rate was significantly higher in the amoxicillin group than in the tetracycline group.

Table 1. Baseline characteristics of patients randomized in the two groups.

Variables		Amoxicillin group	Tetracycline group	P value
Number of subjects		113	115	
Age (mean±SD) and range		41.8±13.96 (19–72)	39.84±14.36 (18–74)	0.29*
Gender	Male	61	56	0.42**
	Female	52	59	
Lost to follow up		2	4	
Cannot tolerate drugs		1	6	
Compliance (taken 80% of tablets)		(110/113)98.23%	(105/115)91.30%	

* Independent Sample T Test;

**Pearson Chi Square Test

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Adverse effects and compliance

Overall, 4 patients in the tetracycline group and 2 patients in the amoxicillin group were lost to follow-up, and no outcome data were available for these patients. Additionally, 6 patients in the tetracycline group and 1 patient in the amoxicillin group could not tolerate the medication, i.e., failed to take at least 80% of the prescribed medication, due to severe adverse effects that started a few days after initiation of the treatment. Adverse effects included tolerable diarrhea, bad taste, dizziness, weakness, nausea, skin rash, fever, fatigue, and vomiting, which were reported by 43.4% (49 of 113) of the patients in the amoxicillin group and 65.2% (75 of 115) of the patients in the tetracycline group, and adverse effects were significantly more frequent in the tetracycline group ($p = 0.001$). Bad taste was the most common side effect in both groups, whereas the frequency of vomiting was significantly higher in the tetracycline treatment group (4 vs. 0 in tetracycline vs. amoxicillin groups; $p = 0.04$). A summary of adverse effects in this study is presented in [Table 3](#).

Discussion

Results of this open-label randomized study revealed that substitution of tetracycline with high-dose amoxicillin in classic bismuth-based quadruple therapy can increase *H. pylori* eradication rate and compliance in patients with duodenal ulcer. In patients who received high-dose amoxicillin in bismuth-based quadruple therapy, the eradication rates were 95.6% and 92.9% by the PP and ITT analyses, respectively. Conversely, the eradication rates in patients who received classic bismuth-based quadruple therapy were 83.3% and 75% by PP and ITT analyses, respectively. These findings indicated that substitution of tetracycline with high-dose amoxicillin significantly increased the eradication rate not only by the ITT analysis but also the PP analysis. As more than 50% of *H. pylori* strains in Iran are resistant to metronidazole [6–8], amoxicillin might achieve better synergistic effects with metronidazole than tetracycline for eradication of metronidazole-resistant *H. pylori* strains. Additionally, patients had better tolerance to bismuth-based quadruple therapy containing amoxicillin instead of tetracycline.

Generally, management of disorders associated with *H. pylori* infection requires treatment regimens that have eradication rates of more than 90% to 95%, if possible [18]. Use of similar effective first-line treatments is important not only for disease cure but also for prevention of secondary antibiotic resistance [19].

A recent review of various regimens used as primary treatment in West Asia suggested that bismuth-furazolidone-metronidazole treatment for 10 days, clarithromycin-based hybrid

CONSORT Flow Diagram

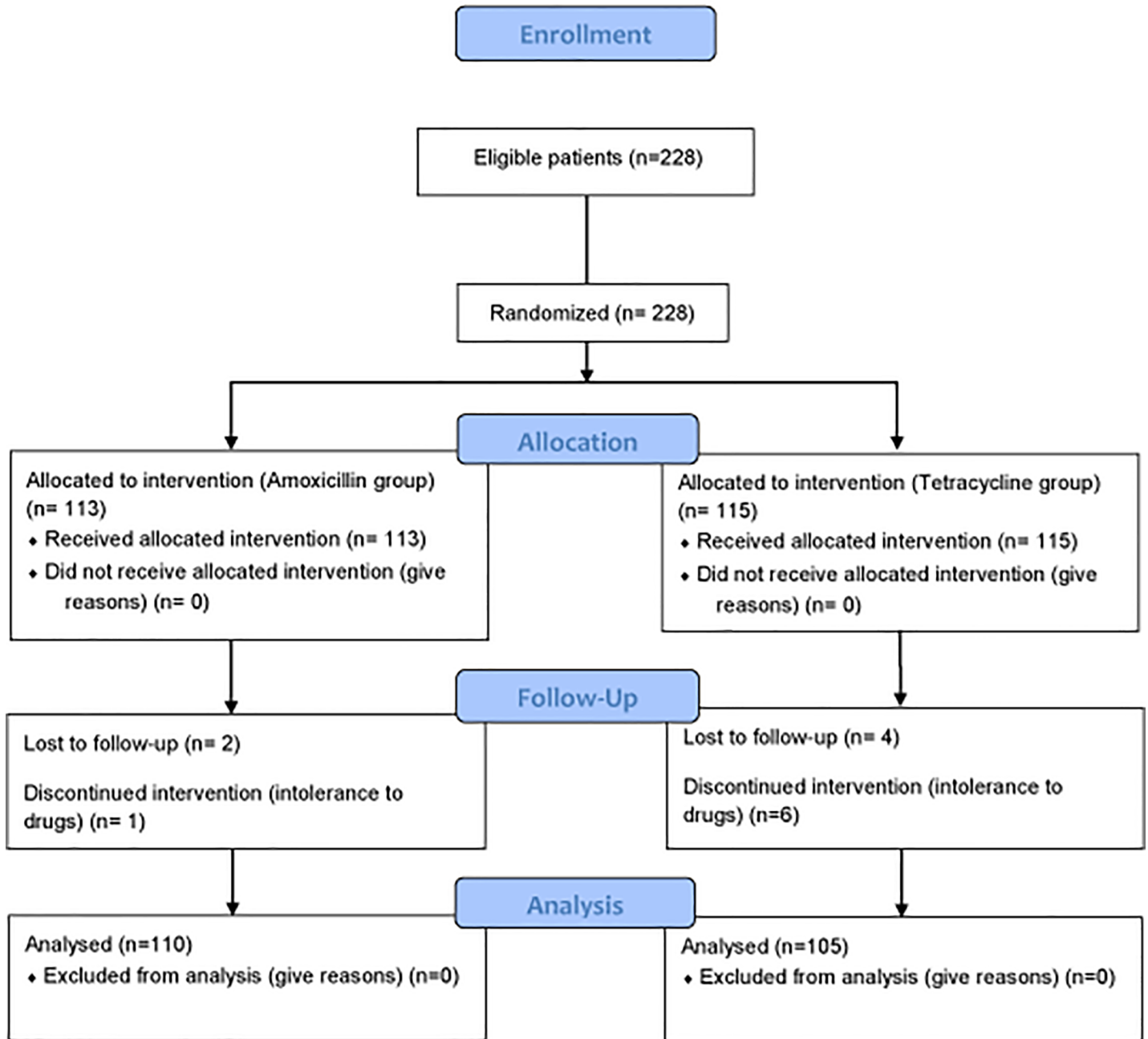


Fig 1. CONSORT flow diagram.

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treatment for 14 days, and classic bismuth-based quadruple therapy including PPIs, bismuth, tetracycline, and metronidazole for 14 days, were equally effective [20]. Since the furazolidone-based regimen has many side effects, the regimen containing adequate-dose furazolidone

Table 2. H.pylorieradication rates in intention-to-treat and per-protocol analyses.

Analysis	Amoxicillin group	Tetracycline group	95% CI for difference between amoxicillin and tetracycline group	Mean difference	p value
ITT	92.9% (105/113)	76.5% (88/115)	7.3% to 25.4%	16.3%	0.001*
95% CI	88.1% to 97.6%	68.7% to 84.2%			
PP	95.5% (105/110)	83.8% (88/105)	3.5% to 19.6%	11.6%	0.005*
95% CI	91.5% to 99.3%	76.7% to 90.8%			

*Pearson Chi Square;

ITT: intention-to-treat; PP: per protocol; CI: confidence interval

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(400mg/day) is not recommended [21, 22]. Due to high resistance to clarithromycin, clarithromycin-containing regimen is not acceptable in our treatment course [23]. Potentially high resistance to levofloxacin also limits its use as front-line treatment [9, 23]. *H. pylori* culture and antibiogram are expensive, and lack of information on pretreatment susceptibility to antibiotics is the main reason for bismuth-based quadruple therapy as a primary regimen for eradication of *H. pylori* in our region, as recommended by the Toronto Consensus [24]. Malfertheiner and colleagues showed that in regions with high resistance to clarithromycin, quadruple treatment containing bismuth, metronidazole, tetracycline, and a PPI was preferable as the primary therapy for *H. pylori* eradication. Quadruple therapy achieves superior eradication with safety and tolerability comparable to those obtained with standard triple therapy [25]. In contrast to metronidazole, increase in clarithromycin dose was reported not to increase the eradication rate of clarithromycin-resistant *H. pylori* [26].

Liang *et al.* concluded that four different bismuth-based quadruple treatments exhibited eradication rates of >90% against *H. pylori* in subjects who were unresponsive to prior therapies, including those showing resistance to clarithromycin and metronidazole [27]. Therefore, the two-week bismuth-based quadruple therapy containing high-dose metronidazole, a PPI, and tetracycline is a proper first-line treatment regimen in our patients with duodenal ulcer [28–30]. This regimen requires modifications with respect to drugs, doses, and duration to reach excellent *H. pylori* eradication rates. Bismuth and metronidazole are necessary additions in this regimen. Increase in *H. pylori* eradication rate with an increased metronidazole dose is dependent on the presence of bismuth. Bismuth also improves the elimination of *H. pylori* by triple therapy regimen [31]. In a systematic review and meta-analysis of 35 randomized clinical

Table 3. Side effects of treatment in groups.

Variables	Amoxicillin group	Tetracycline group	P Value*
Tolerable diarrhea	6 (5.3%)	8 (7.0%)	0.60
Bad taste	19 (16.8%)	22 (19.1%)	0.64
Dizziness	3 (2.7%)	4 (3.5%)	0.71
Weakness	4 (3.5%)	6 (5.2%)	0.61
Nausea	9 (8.0%)	17 (14.8%)	0.10
Skin rash	4 (3.5%)	4 (3.5%)	0.98
Fever	2 (1.8%)	3 (2.6%)	0.66
Fatigue	2 (1.8%)	7 (6.1%)	0.09
Vomiting	0 (0%)	4 (3.5%)	0.04
Total side effects % (n)	49 (43.4%)	75 (65.2%)	0.001

*Pearson Chi Square Test

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trials and 4763 subjects, the safety profile of bismuth was assessed, which revealed insignificant side effects in patients undergoing bismuth-based treatment [32]. Emerging evidence of increasing resistance to tetracycline and reports demonstrating that adequate-dose metronidazole in combination with tetracycline results in more side effects raise concerns regarding substitution of tetracycline with another antibiotic.

To achieve increased compliance to classic bismuth-based quadruple therapy, tetracycline was replaced with high-dose amoxicillin, based on several lines of evidence: In a recent study, high-dose amoxicillin (750mg four times a day) in combination with a potent PPI achieved a very good eradication rate, suggesting that amoxicillin is a unique anti-*H. pylori* antibiotic that has an acceptable eradication rate when used as part of a dual therapy containing a PPI [33, 34]. The resistance rates to amoxicillin, metronidazole, and clarithromycin were about 2%, 44%, and 29% in America; 0.7%, 35%, and 18% in Europe; and 2%, 38%, and 21% in Asia, respectively [35]. *H. pylori* was found to rapidly acquire antibiotic resistance to clarithromycin, metronidazole, and levofloxacin but not to amoxicillin after a single course of anti-*H. pylori* therapy [36]. One potential explanation for the difference in acquired antibiotic resistance is that a single-point mutation can lead to resistance to clarithromycin, metronidazole, and levofloxacin, whereas multiple-site mutations are necessary to confer amoxicillin resistance [37–39]. A recent study among US male patients revealed increased resistance to clarithromycin and levofloxacin but no resistance to amoxicillin [40]. In Iran, 1.6%, 16.7%, and 57.5% of *H. pylori* strains showed resistance to amoxicillin, clarithromycin, and metronidazole, respectively; however, no tetracycline resistance was reported [41]. However, this sensitivity pattern was found to have changed five years later, and there is an increasing resistance to tetracycline [42]. A recent study in Yazd, Iran revealed that *H. pylori* is more resistant to tetracycline than amoxicillin [43]. In a study in China, amoxicillin, in combination with metronidazole, bismuth, and lansoprazole, eradicated metronidazole-resistant *H. pylori*. In their study, Zhang *et al.* used 2g amoxicillin per day in combination with lansoprazole, metronidazole, and bismuth [44]. Lansoprazole, albeit more potent, is more expensive than omeprazole in Iran; therefore, high-dose amoxicillin with omeprazole was preferred over 2g amoxicillin with lansoprazole.

The ITT analysis revealed an eradication rate of 92.92% in the amoxicillin group compared with the rate of 76.5% in the tetracycline group, indicating that bismuth-based quadruple therapy containing tetracycline with adequate-dose metronidazole was associated with more adverse effects and intolerance. Unfortunately, severe adverse effects that lead to intolerance in the tetracycline group occurred 4–5 days after treatment initiation. In contrast, there were no severe drug-associated complications with the high-dose amoxicillin regimen, and the patient compliance was good.

Inability to evaluate the *H. pylori* antimicrobial resistance patterns was one of the main limitations of this study; however a recent regional study indicated that *H. pylori* resistance to tetracycline was more common than that to amoxicillin, which might explain the 16% failure rate in the tetracycline group compared to the 5% failure rate in the amoxicillin group based on the PP analysis [43].

Conclusion

The results of this randomized, open-label clinical trial revealed that a two-week bismuth-based quadruple therapy including high-dose amoxicillin and metronidazole had an acceptable eradication rate with good tolerance in patients with duodenal ulcer and *H. pylori* infection. This therapy might overcome treatment resistance in areas with high prevalence of *H. pylori* resistance to metronidazole and clarithromycin.

Supporting information

S1 Checklist. CONSORT 2010 checklist.

(DOC)

S1 File. Study protocol.

(DOC)

S2 File. Ethic approval.

(PDF)

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