Original Article

Inefficacy of Triple Therapy and Comparison of Two Different Bismuth-containing Quadruple Regimens as a Firstline Treatment Option for *Helicobacter pylori*

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ABSTRACT

Background/Aim: Increasing resistance of *Helicobacter pylori* to antimicrobials necessitated the development of new regimens and the modification of existing regimens. The present study aimed to compare the efficacy of two bismuth-containing quadruple regimens—one including clarithromycin (C) instead of metronidazole (M) and triple therapy. **Patients and Methods:** Patients with *H. pylori* infection given the following regimens were sequentially enrolled in this retrospective study: (1) Triple therapy: Lansoprazole 30 mg b.i.d., clarithromycin 500 mg b.i.d., and amoxicillin 1 g b.i.d., (2) bismuth group C: Lansoprazole 30 mg b.i.d., clarithromycin 500 mg b.i.d., amoxicillin 1 g b.i.d., and bismuth subsalicylate 524 mg b.i.d., and (3) bismuth group M: Lansoprazole 30 mg b.i.d., amoxicillin 1 g b.i.d., metronidazole 500 mg t.i.d., and bismuth subsalicylate 524 mg b.i.d. for 14 days. Gastroscopy and ^{14}C-urea breath test were performed before enrollment, and urea breath test was repeated four weeks after the treatment. **Results:** At per-protocol analysis, the eradication rates were 64.7% (95% confidence interval 60.4–68.7) with the triple therapy (n = 504), 95.4% (95% confidence interval 91.5–99.4) with the bismuth group C (n = 501), and 93.9% (95% confidence interval 89.7–98.7) with the bismuth group M (n = 505). The eradication rates were similar between the two bismuth groups ($P > 0.05$) but significantly greater than that of the triple therapy ($P < 0.05$). **Conclusion:** In our study, both of the bismuth-containing quadruple therapies reached high eradication rates, whereas triple therapy was shown to be ineffective. Moreover, clarithromycin may also be a component of bismuth-containing quadruple therapy.

Key Words: Bismuth, clarithromycin, eradication, *Helicobacter pylori*, metronidazole

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Helicobacter pylori infection is a worldwide problem. Eighty percent of the population in developing countries and 20%–50% of the population in the developed countries are estimated to carry this pathogen.[1-3] The ultimate clinical manifestations of *H. pylori* infection include gastric and duodenal ulcer, gastric mucosa–associated lymphoid tissue lymphoma, and adenocarcinoma.[4,5] *H. pylori* eradication remains a challenge for the physicians, since no firstline regimen is able to cure the infection in all treated patients due to antibiotic resistance. The efficacy of standard triple therapy has decreased recently and is less than the 80% rate aimed for at the beginning.[5-8] The background rate of clarithromycin resistance is critically important as its presence negatively impacts the efficacy of standard triple therapy.[9] For this reason bismuth-containing quadruple therapies are recommended for firstline empirical treatment in areas of high clarithromycin resistance (>15%–20%) according to Maastricht IV consensus report.[8]

It is known that resistance to metronidazole can be partially overcome by increased dose and duration of treatment.[10]

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This multicenter study aimed to perform a comparison among two bismuth-containing quadruple therapies—one including clarithromycin (C) instead of metronidazole (M) and triple therapy for *H. pylori* eradication in dyspeptic patients.

PATIENTS AND METHODS

Patients

This study was a retrospective research. The study was undertaken in the gastroenterology and internal medicine outpatient clinics of Çorum State Hospital, Ankara Education and Research Hospital and Ankara Oncology Education and Research Hospital, Turkey, between August 2012 and April 2015. Local Ethics Committee for Human Studies approved the protocol. Patients complaining of dyspeptic symptoms referred for upper endoscopy were included in this study. At the beginning, all patients underwent endoscopy with biopsies for histology (two samples from the antrum and one sample from the gastric body) and the diagnosis of active *H. pylori* infection was made based on the presence of two positive tests consisting of histology with Giemsa and hematoxylin and eosin stain, and urea breath test (^{14}C-UBT) or rapid urease test (one sample from the antrum).

The following cases were excluded from the study: Age <18 years, those who had ingested bismuth, antibiotics, antisecretory medication, or proton pump inhibitors (PPI) during the four weeks prior to endoscopy; those who were pregnant or immunocompromised, those who had coexisting gastric cancer, those who had a history of gastric surgery, or a previous attempt to eradicate *H. pylori* and known allergy to antibiotics. All procedures were performed after obtaining informed consent from the patients.

The patients were treated with the triple or bismuth-containing quadruple eradication therapies based on preferences of their physicians as such: (1) Triple therapy: Lansoprazole 30 mg b.i.d., clarithromycin 500 mg b.i.d., and amoxicillin 1 g b.i.d., (2) bismuth group C: Lansoprazole 30 mg b.i.d., clarithromycin 500 mg b.i.d., amoxicillin 1 g b.i.d., and bismuth subsalicylate 524 mg b.i.d., and (3) bismuth group M: Lansoprazole 30 mg b.i.d., amoxicillin 1 g b.i.d., metronidazole 500 mg t.i.d., and bismuth subsalicylate 524 mg b.i.d. for 14 days. *H. pylori* eradication was determined via the ^{14}C-UBT performed four weeks after the end of therapy. Patients were asked to avoid antiacid treatment and antibiotics for 1 month before performing ^{14}C-UBT.

Statistical analyses

Data were analyzed by using the *t*-test for unpaired data, and Chi-square test, as appropriate. The eradication rates of *H. pylori* with their 95% confidence intervals (95% CI) could be assessed only on the basis of per-protocol analysis (PP - the number of patients adherent to the protocol) due to retrospective nature of the study and differences were considered significant at a 5% probability level. The statistical analysis was performed using SPSS software (Statistical Package for the Social Sciences, version 18.0, SSPS Inc., Chicago, IL, USA).

RESULTS

One thousand five hundred and ten consecutive patients who adhered to their therapeutic regimens were enrolled in the study. The baseline demographic and clinical characteristics of each group were comparable [Table 1]. *H. pylori* eradication was achieved in 326 out of 504 patients (64.7%) in the triple therapy group, 478 out of 501 patients (95.4%) in the bismuth group C, and 474 out of 505 (93.9%) in the bismuth group M. *H. pylori* eradication rates along with 95% CI and *P* values between the groups are provided in Table 2. Accordingly, both bismuth regimens achieved significantly better eradication rates compared with the triple therapy group, whereas the difference between the bismuth C and bismuth M groups was not significant [Table 2].

Regarding tolerable side effects, 22 (4.4%), 21 (4.1%), and 23 (4.5%) patients complained of one or more side effects following triple, bismuth C, and bismuth M therapies, respectively ($P > 0.05$, Table 3). Intolerable side effects leading to interruption of therapy were as follows: (1) Triple therapy group ($n = 12$, 2.3%): Abdominal discomfort and vomiting ($n = 8$), diarrhea ($n = 3$), and skin rash ($n = 1$). (2) Bismuth group C ($n = 14$, 2.9%): Metallic taste and vomiting ($n = 14$). (3) Bismuth group M ($n = 11$, 2.2%): Abdominal discomfort ($n = 5$), vomiting ($n = 3$), diarrhea ($n = 2$), and dizziness ($n = 1$).

Table 1: Demographic characteristics of the patients

	Triple therapy	Bismuth C	Bismuth M
Number of patients	504	501	505
Age (years) (mean±SD)	40.3±0.6	40.0±0.6	40.7±0.6
Sex % (M/F)	42.5/57.5	31.1/68.9	46.5/53.5
Smoking habit % (Y/N)	37.7/62.3	22.4/77.6	30.9/66.1

C: Clarythromycin, M: Metronidazole

Table 2: *H. Pylori* eradication rates after bismuth containing quadruple and triple *H. Pylori* eradication regimens

	Triple	*P*[a]	Bismuth C	*p*	Bismuth M
PP analysis	326/504	<0.0001	478/501	0.276	474/505
n (%)	64.7)		(95.4)		(93.9)
(95% CI)	(60.4-68.7)		(91.5-99.4)		(89.7-98.7)

PP: Per protocol, C: Clarythromycin, M: Metronidazole. [a]Bismuth C vs triple and bismuth M vs triple therapy

Table 3: Side effects of bismuth containing quadruple and triple *H. Pylori* eradication regimens

Side effects	Triple (*n*=504)	Bismuth C (*n*=501)	Bismuth M (*n*=505)
Abdominal pain	4	4	5
Diarrhea	4	2	1
Constipation	-	2	3
Nausea	5	4	5
Vomiting	2	2	0
Metallic taste	5	2	4
Skin rash	2	1	-
Pruritus	2	2	1
Asthenia	-	-	1
Fatique	1	2	3
Number of patients	22	21	23

Some patients had one or more side effects C: Clarythromycin, M: Metronidazole

DISCUSSION

Random mutations in the *H. pylori* 23S ribosome gene can prevent binding of clarithromycin so that it is no longer effective. Similarly, nitroimidazoles are no longer metabolized to its bacteria-toxic form when a random mutation inactivates the *rdx*A gene.[11] Imidazole and clarithromycin resistance in recent years has called into question the efficacy of the regimens including these antimicrobial agents. The primary *H. pylori* clarithromycin resistance rate was reported as 16.3%–50% in central region (city Ankara) of Turkey. On the other hand the primary *H. pylori* metronidazole resistance rate was reported as 39.2% in near part of Ankara. In clarithromycin resistance development, three point mutations may occur at the two nucleotide positions 2142 (A2142G and A2142C) and 2143 (A2143G) in the 23S rRNA gene. The point mutations responsible for clarithromycin resistance were detected as A2143G and A2144G in Turkish studies.[9]

In adult dyspeptic Turkish patients, Onder *et al.*[12] found clarithromycin resistance to be 48.2%. Our study showed that eradication success could still be achieved with bismuth-based quadruple therapies in an area with high prevalence of clarithromycin and metronidazole resistance. Another observation was that a substantial number of patients were still being prescribed the triple therapy. But our results once again showed that this regimen had an unacceptable eradication failure rate and it should no more be the first choice in countries with a high *H. pylori* resistance rate to clarithromycin.[12]

Alternative strategies have been proposed to overcome *H. pylori* resistance to antibiotics, and some of them are already implemented in clinical practice. These are the development of more effective empirical treatments, a tailored therapeutic approach based on pre-treatment determination of *H. pylori* therapeutic susceptibility and adjunct use of probiotics to improve eradication rates. Among these strategies the most preferred one has been the investigation of new therapeutic regimens. At present, the largely validated firstline regimens are bismuth containing quadruple therapy and concomitant, sequential, and hybrid therapies.[13] Standard triple therapy is only suitable for areas of <20% incidence of clarithromycin resistance or tailored treatment.[13] However, tailored therapy for *H. pylori* commonly is not currently available because culture of *H. pylori* is costly, time consuming, complicated, and offered by only a few laboratories. Levofloxacin- or rifabutin-based triple therapies are recommended as secondline/rescue therapies.[13]

Bismuth-containing quadruple therapies may be modified with respect to their antimicrobial components other than bismuth. Liang *et al.* showed that four bismuth and PPI-containing quadruple therapies additionally including the combination of tetracycline–metronidazole, tetracycline–furazolidone, tetracycline–amoxicillin, or amoxicillin–furazolidone achieved greater than 90% eradication of *H. pylori* in patients who did not respond to previous treatment, including patients with clarithromycin-, metronidazole-, and fluoroquinolone-resistance.[14] Our study provides additional information that clarithromycin can also be an option in the context of bismuth-based quadruple therapies. On the other hand as dual resistance of *H. pylori* to metronidazole and clarithromycin has been seen in our population rarely, using them together would probably be a poor choice. Another important parameter is the duration of treatment which should be 14 days. Previous experiences in our population have shown that 7–10 day treatment with current eradication regimens does not achieve an optimum eradication rate.[15]

The frequency of adverse effects and compliance to treatment can significantly affect the success of anti-*H. pylori* treatment regimens. In our series the proportion of patients with major and minor side effects were less than 10%. We think that this rate of side effects is acceptable taking into consideration that the two bismuth-based regimens have an efficacy higher than 90%.

The present study has several limitations. One of the most important limitations is that no culture for *H. pylori* was performed, and therefore the susceptibility/resistance rates were unknown. Another limitation of this study is its retrospective nature. Moreover, heterogeneity in the methods is another potential limitation.

In summary, bismuth-containing quadruple therapies are effective eradication regimens, whereas triple therapy was shown to be ineffective in our population. Additionally,

clarithromycin may also be preferred as a component of this regimen. Further studies are required to reveal new agents or combinations as part of bismuth-based quadruple regimens so that physicians may be more flexible to modify these regimens according to the local resistance pattern and side effect profile.

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Conflicts of interest

There are no conflicts of interest.

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