Original Article

Levofloxacin-containing versus Clarithromycin-containing Therapy for *Helicobacter pylori* Eradication: A Prospective Randomized Controlled Clinical Trial

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Abstract

Background: This study evaluated the clinical efficacy and tolerability of a 14-day course of bismuth-based quadruple therapy including tinidazole and levofloxacin in compare to a 14-day bismuth-based quadruple therapy including clarithromycin as first-line treatment for *Helicobacter pylori* infection in Iranian adults. **Materials and Methods:** The study was a prospective, parallel group, randomized controlled, clinical trial that conducted on 150 patients with *H. pylori* infection. Patients were randomly assigned to the two groups as follows: first group received pantoprazole 40 mg, bismuth subcitrate 240 mg, amoxicillin 1 g, and clarithromycin 500 mg (PBAC group), and other group received pantoprazole 40 mg, bismuth subcitrate 240 mg, amoxicillin 1 g, tinidazole 500 mg for 7 days, followed by levofloxacin 500 mg for the second 7 days (PBATL group). Main outcomes were eradication rate, tolerance of treatment, and dyspepsia severity. **Results:** The eradication rates for PBAC regimen was 81.1% (95% confidence interval [CI]: 71.9–90.2) and for PBATL regimen was 70.8% (95% CI: 60.1–81.6), which was not significantly different ($P = 0.147$). Tolerance of treatment was similar between groups. The median of severity of dyspeptic after treatment in PBAC group was 10 [9–14.75], which was similar to PBATL group 10 [9–13.5] ($P = 0.690$). **Conclusion:** There is no significant difference between PBAC and PBATL regimen, and efficacy was similar in both groups. The overall rate of treatment failure suggests that up to 18%–30% of patients will fail bismuth-based quadruple therapy and require retreatment for the infection.

Keywords: *Clarithromycin, Helicobacter pylori, levofloxacin, tinidazole*

Introduction

Helicobacter pylorus has been linked conclusively to various disorders of the upper gastrointestinal tract, including peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer.[1,2] Approximately over half of the world's population is reported to have *H. pylori* infection and depending on the population studied, infects 7% to 87% of adults.[3,4] A global systematic review shows that approximately 4.4 billion people in the world were estimated to be infected with for *H. pylori* in 2015. This infection is more common in developing countries, and in Asia, 54.7% reported to be positive for *H. pylori*. In Iran, analyses of reports show that 59% of people were infected by *H. pylori*.[5]

Choosing a treatment for *H. pylori* eradication depends on different factors, such as the local availability of antimicrobial agents, the pattern of primary antibiotic resistance, and the therapeutic cost.[3] The most commonly recommended for first-line treatment of *H. pylori* included 7- to 14-day triple therapy with a proton-pump inhibitor (PPI), amoxicillin, and clarithromycin with cure rates of 80%–90%.[6,7] These rates were reported for many years ago, and studies from different parts of the world have raised some important concerns about the current success of this regimen, especially with regard to increasing clarithromycin resistance.[8,9] Thus, bismuth-containing quadruple therapy is recommended as first-line treatment for the eradication of *H. pylori* infection in regions with a high clarithromycin resistance rate. In Iran with increasing in clarithromycin resistance rate, bismuth-containing quadruple therapy has been strongly recommended.

Levofloxacin and tinidazole have been shown to be effective for the treatment

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of *H. pylori* infection, and some studies have also shown that these drugs are effective as the first-line treatment for *H. pylori* eradication.[10-12] The optimal duration for *H. pylori* eradication therapy is controversial, with recommendations ranging from 7 to 14 days whereas the duration of therapy with the pattern of *H. pylori* antibiotic resistance, and the patients' compliance is known as the main factors in the success rate of eradication regimens.[13] In regard to the high resistance to metronidazole and clarithromycin in patients infected by *H. pylori* in Iran and controversial findings on the therapy, the present study was designed to investigate effective treatment duration for 14-day bismuth-based quadruple therapy including tinidazole (for 7 days), followed by levofloxacin (for 7 days) in compare to 14-day bismuth-based quadruple therapy including clarithromycin by comparing eradication rate, compliance, and adverse event rate between the regimens as first-line treatment for *H. pylori* eradication.

Materials and Methods

The study was a prospective, parallel group, randomized controlled, clinical trial that conducted on 150 patients, referrals to the gastroenterology clinics of Isfahan University of Medical Sciences (IUMS) from February to November 2016. Ethical approval was obtained from the Research Ethics Committee of IUMS before recruitment.

One hundred fifty consecutive patients were included in the study according to the following inclusion criteria: (1) patients in both genders with age 18 and over and (2) patients with peptic ulcer disease. *H. pylori* infection was confirmed by serologic and gastric tissue. The participants with known gastrointestinal malignancy, MALT lymphoma, Zollinger–Ellison syndrome, immunodeficiency disorders, liver or renal diseases, clinical conditions that need antibiotic therapy, history of gastric surgery, and history of *H. pylori* eradication or using PPI, antibiotic, or probiotics within 4 weeks before the study and pregnant women were not included in the study. The exclusion criteria were serious side effects that require immediate discontinuation of therapy. Furthermore, patients who did not use their study medications regularly were excluded from the study.

All eligible patients were voluntary and gave written informed consent to participate in the study. The sampling method was consecutive, and randomization was performed by generating a random list of patient allocations before the start of intervention, by Random Allocation Software.

Enrolled patients were randomly assigned to one of the two equal groups. Group I (PBAC) had 75 patients who received treatment regimen included pantoprazole 40 mg, bismuth subcitrate 240 mg, amoxicillin 1 g, and clarithromycin 500 mg; all given twice daily (q12 h) for 14 days. Group II (PBATL) had 75 patients who received treatment regimen included pantoprazole 40 mg, bismuth subcitrate 240 mg, amoxicillin 1 g, twice/day for 14 days, tinidazole 500 mg twice daily for the first 7 days, followed by levofloxacin 500 mg daily for the second 7 days.

Collected data included age, sex, dyspepsia symptoms, medicinal effects of each regimen (bad taste, nausea, bloating, diarrhea, constipation, skin rash, and epigastric pain); intolerance of treatment which was assessed at the end of treatment as none, mild, moderate, and severe; and eradication rate. To assess the eradication rate of *H. pylori* in studied patients, 13C urea breath test with 94% of sensitivity and 95% of specificity, respectively, was use 1 month after the end of treatments.[14] Dyspepsia severity was evaluated by the short-form leeds dyspepsia questionnaire (SFLDQ), which evaluates frequency and interference of four symptoms including epigastric pain/discomfort, retrosternal burning, regurgitation, and nausea. The total score of the SFLDQ ranges from 0 to 32 and was completed by patients in both groups at baseline and after treatment.[15]

Statistical analyses were done using SPSS software for Windows (SPSS, Inc., Chicago, IL, USA, version 24). Descriptive data are reported as mean ± standard deviation, median (IQR), or number (percent) as appropriate. Independent sample *t*-test, Chi-square test, Mann–Whitney U-test, Wilcoxon signed-rank test, and analysis of covariance (ANCOVA) were used as appropriate. All hypothesis testing was two tailed, and level of significance was considered to be <0.05 in all tests.

Results

One hundred sixty patients were reviewed to selected eligible patients; ten patients did not enter (nine refused informed consent and one was not eligible). One hundred fifty eligible patients randomly allocated into two intervention groups. Four patients were lost during follow-up period. Finally, 74 patients in PBAC group and 72 patients in PBATL group completed the study and analyzed [Figure 1].

The mean age of studied participants was 47.3 ± 12.8 years; 44.5% (65 patients) were male and 55.5% (81 patients) were female. Other demographics and clinical characteristics of the participants by treatment regimens are shown in Table 1.

As shown in Table 2, there has been significant reduction in the LDQ score in both regimens. The result of ANCOVA was not found any difference between groups.

There was no significant difference of *H. pylori* eradication rates between the studied regimens. The eradication rate for PBAC regimen was 81.1% (95% confidence interval [CI]: 71.9–90.2) and for PBATL regimen was 70.8% (95% CI: 60.1–81.6) ($P = 0.147$).

In this study, overall HP eradication rate was significantly associated with age. The whole observations indicate that younger patients had a significantly better

response [Table 3 and Figure 2]. However, there was no significant difference between the regimens by age for the *H. pylori* eradication rates ($P > 0.05$).

Discussion

In this study, PBAC regimen included 14-day treatment with bismuth, amoxicillin, clarithromycin, and pantoprazole which was associated with higher rates of *H. pylori* eradication in compare to PBATL regimen included 14-day treatment with bismuth, amoxicillin, tinidazole (followed by levofloxacin in the second 7 days), and pantoprazole. Eradication rate for PBAC regimen was 81.1% and for PBATL regimen was 70.8%, which did not significantly differ between groups. There is no significantly different for adverse event between groups, and both studied regimens were well tolerated based on patients' reports in two studied groups. The rates of eradication in

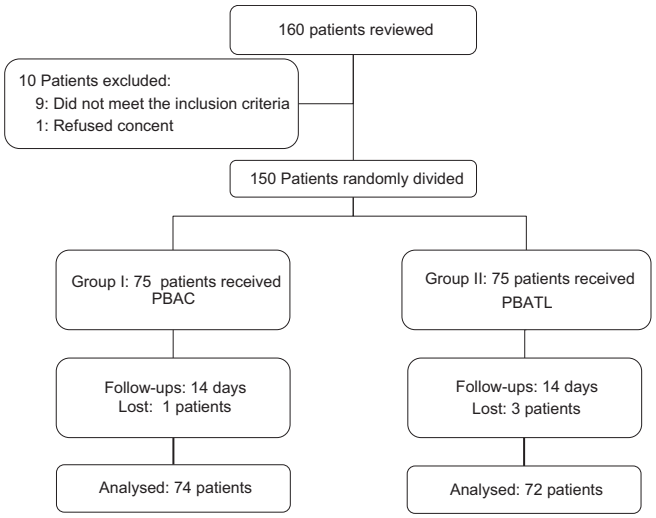

Figure 1: Flow diagram of patient's recruitment

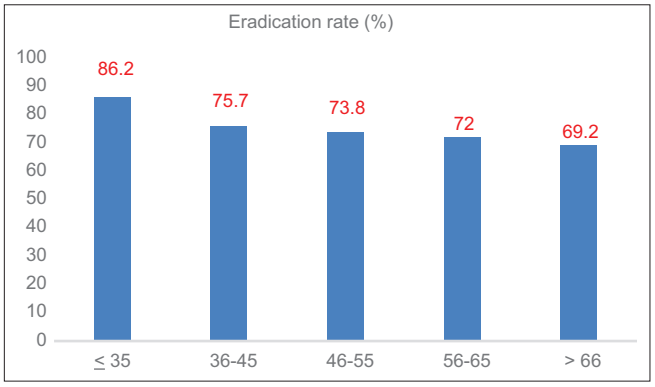

Figure 2: Overall *Helicobacter pylori* eradication in studied population by age group

Table 1: Demographic and clinical characteristics of studied population by intervention groups

Characteristics	Groups		*P*
	14-day PBATL (*n*=72)	14-day PBAC (*n*=74)	
Age (year)	47.3±12.7	47.2±12.9	0.961*
Gender			
Female	38 (52.8)	43 (58.1)	0.517†
Baseline endoscopic findings			
Gastric ulcer	5 (6.9)	7 (9.5)	0.589†
Duodenal ulcer	33 (45.8)	28 (37.8)	
Dyspepsia	34 (47.2)	39 (52.7)	
HP test to diagnose			
Serology	4	9	0.236†
Biopsy-based test	65	58	
Urea breath test	2	3	
Stool antigen test	1	4	
Tolerance of treatment	55 (76.4)	57 (77.0)	0.912†
Intolerance (mild/moderate/severe)	8/5/4	12/5/0	0.091†
Self-reported adverse event	44 (61.1)	35 (47.3)	
Bad taste	21 (29.2)	20 (27.0)	0.132† (NS)
Nausea	4 (5.6)	4 (5.4)	
Bloating	1 (1.4)	1 (1.4)	
Diarrhea	8 (11.1)	5 (6.8)	
Constipation	3 (4.2)	3 (4.1)	
Skin rash	2 (2.8)	0	
Epigastric pain	5 (6.9)	2 (2.7)	
Eradication rate	51 (70.8)	60 (81.1)	0.147†

The data are presented as mean±SD or number (percent). *P* values calculated by *Independent sample *t*-test and †Chi-square test.
HP: *Helicobacter pylori*, NS: Nonsignificant, LDQ: Leeds dyspepsia questionnaire, IQR: Interquartile range, SD: Standard deviation, PBATL: Regimen based on pantoprazole, bismuth subcitrate, amoxicillin and (tinidazole/levofloxacin), PBAC: Regimen based on pantoprazole, bismuth subcitrate, amoxicillin and clarithromycin

our studied regimens were low, and according to Graham classified efficacy of *H. pylori* treatment,[15,16] success rate in PBATL regimen is poor and for PBAC regimen is unacceptable. The lower rate of eradication in our study might be related to the prevalence of antibiotic resistant of *H. pylori* strains in our studied patients, where we did not assess pretreatment antibiotic resistant in these patients.

In a meta-analysis, it is reported that sequential therapy was superior to a 7-day standard triple therapy regimen, but when compared with a longer duration of standard triple therapy, the difference disappeared.[17] In the other studies, the duration of sequential therapy has been assessed to determine whether longer therapy will help improve the eradication rates of *H. pylori* infection. In Warrington *et al*. study, it is shown that regardless of the treatment duration, sequential regimens are not better than standard triple therapy. In this study, the eradication rate was 83.7% in the standard triple therapy, 80.0% in the 10-day sequential therapy, and 79.1% in the 14-day sequential therapy regimen.[18] In a large study by Liou *et al*., it is suggested that longer therapy with a sequential regimen would provide better eradication rates. In these study for 10- and 14-day of sequential therapy, the eradication rate of 90.7% and 87.0% is reported, respectively, and in a 14-day standard triple therapy group, the eradication rate was 82.3%.[19] In Ergül *et al*.'s study, eradication rate of 90.7% is reported for a 14-day bismuth-containing quadruple therapy as first-line therapy.[20] Su *et al*. in their study showed an eradication rate of 80.2% and 89.7% for 1-week two regimens of bismuth-based quadruple-containing clarithromycin or levofloxacin, respectively.[21] One study in Iranian patients reported 82.3% of eradication rate of *H. pylori* for quadruple therapy after 2 weeks.[22] In another report from Iran, after 10-day quadruple therapy, eradication rate was 84.0%.[23] In the Mousavi *et al*. study, 14 days of bismuth-based quadruple regimen had eradication rate of 75.7%.[24] Aminian *et al*. reported 85.7% of *H. pylori* eradication rate after 4 days of bismuth-based quadruple with metronidazole.[25] In a randomized clinical trial, Metanat *et al*. evaluated 10- and 14-day nonbismuth-based quadruple regimen for *H. pylori* treatment and reported eradication rate 83.5% and 92.8% for studied regimens, respectively.[26] In the present study, in both bismuth-based quadruple therapy, eradication rates were lower than reported previously (81.1% for PBAC regimen and 70.8% for PBATL regimen). The prevalence of antibiotic resistance, differences in the studied regimens, and does of drugs might be explain the differences between study findings.

Table 2: The summary results of both frequency and severity of dyspeptic symptoms based on Leeds dyspepsia questionnaire score according to treatment regimens

HP treatment regimens	Baseline	After	P^b	P^c
14-day PBATL	18 (14-26.75)	10 (9-14.75)	<0.0001	0.690
14-day PBAC	18 (14-26.5)	10 (9-13.5)	<0.0001	
P^a	0.729	0.576		

Data expressed as median (IQR). [a]*P*: Assessed LDQ score between groups at each time points; calculated by Mann–Whitney U-test, [b]*P*: Assessed LDQ score within groups after treatment compare to baseline; calculated by Wilcoxon signed-rank test, [c]*P*: Assessed LDQ score between treatment groups by ANCOVA (baseline value as covariate). HP: Helicobacter pylori, LDQ: Leeds dyspepsia questionnaire, PBAC: Regimen based on pantoprazole, bismuth subcitrate, amoxicillin and clarithromycin, PBATL: Regimen based on pantoprazole, bismuth subcitrate, amoxicillin and (tinidazole/levofloxacin), ANCOVA: Analysis of covariance, IQR: Interquartile range

In the present study, the eradication rate was decreased with increase in age group; patients in older age group had a lower rate of eradication though this difference was not statistically significant. In other study, in Iran, it is reported that patients' age and gender are associated with *H. pylori* eradication rate.[22] Another study reported that occupation, gender, and protocol compliance were positively associated with *H. pylori* eradication rate.[27] Silva *et al*. report a significant association between age and *H. pylori* eradication rate but did not report a significant difference between patients' characteristics and eradication rate.[28]

The present study has some limitations. First is the lack of any analysis of antibiotic resistance relative to the eradication rates and treatment regimens, whereas antibiotic resistance is known as the most important cause of treatment failure. Second, this trial was not a double-blind placebo-controlled trial in which the detection bias was minimized. Third, this study was a single-center study and its results need to be externally validated.

Conclusion

This randomized trial showed that a 14-day bismuth-based quadruple regimen-containing amoxicillin, tinidazole (followed by levofloxacin in the second 7 days), and pantoprazole is statistically effective as well as 14-day bismuth-based quadruple regimen-containing amoxicillin,

Table 3: *Helicobacter pylori* eradication in studied population by age group

Index	Age group					Total
	≤35	36-45	46-55	56-65	>66	
Number of patients	29	37	42	25	13	
Eradication rate (%)	86.2	75.7	73.8	72.0	69.2	76
95% CI	72.9-99.6	61.2-90.2	59.9-87.7	53.1-90.9	40.2-98.3	69-83

clarithromycin, and pantoprazole in the eradication of *H. pylori* infection, and there is no significant difference between PBAC and PBATL regimens. The overall rate of treatment failure suggests that up to 18%–30% of patients will fail bismuth-based quadruple therapy and require retreatment for the infection. More studies are needed to draw meaningful conclusions for optimal duration of *H. pylori* eradication regimens.

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Conflicts of interest

There are no conflicts of interest.

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