

Original Article

A Prospective, Randomized Study Comparing 7-day and 14-day Quadruple Therapies as First-line Treatments for *Helicobacter pylori* Infection in Patients with Functional Dyspepsia

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INTRODUCTION

Helicobacter pylori is one of the most common bacterial pathogens in humans, the only known host of this bacterium. One of the major risk factors for gastric cancer, *H. pylori* also causes many different gastrointestinal diseases such as chronic gastritis, peptic ulcer disease, and lymphoproliferative disorders. *H. pylori* infection is now recognized as a worldwide problem^[1] and was accepted as a grade 1 carcinogen in 1994 by the World Health Organization.^[2] In addition, *H. pylori* infection influences gastric function, including gastric acid secretion, and alters the intragastric environment.^[3] An association between *H. pylori* infection and some diseases occurring outside the gastrointestinal tract, such as idiopathic thrombocytopenic purpura and iron-deficiency anemia, have also been indicated.^[4,5] Although

ABSTRACT

Objective: Standard triple therapy for *Helicobacter pylori* has a low eradication rate in Turkey. The aim of this study was to evaluate and compare the effectiveness of 7-day and 14-day lansoprazole, amoxicillin, clarithromycin, and bismuth subsalicylate (LACB) treatment regimens as first-line *H. pylori* eradication therapies. **Materials and Methods:** This study included 70 patients with symptoms of dyspepsia and a positive *H. pylori* stool antigen test (SAT). Thirty-five patients received the modified quadruple therapy regimen for 7 days (LACB-7) whereas the remaining 35 patients received the treatment for 14 days (LACB-14). Eradication was assessed by SAT 1 month after the end of therapy. **Results:** A total of 64 patients completed the therapy. The cumulative per-protocol (PP) and intention-to-treat (ITT) eradication rates were 89% ($n = 57/64$) and 81.4% ($n = 57/70$), respectively. Both the PP and ITT eradication rates were superior in the LACB-14 group, compared with the LACB-7 group (PP: 90.6% vs. 87.5%; ITT: 81.4% vs. 80%, respectively), but these differences were not statistically significant ($P = 0.689$). **Conclusions:** Both the 7-day and 14-day first-line LACB therapies provided a high cure rate, were well tolerated, and were equally effective against *H. pylori* infection in Turkey.

KEYWORDS: Duodenum, dyspepsia, *Helicobacter pylori*, gastritis, stomach

not all of those infected develop these diseases, they do form a high-risk population for such complications. Therefore, the Maastricht Consensus Report from the European *H. pylori* Study Group advocates the testing for and eradication of *H. pylori* among a variety of patients presenting with gastrointestinal symptoms.^[6]

Although the prevalence of *H. pylori* is decreasing in developed countries, it is increasing in developing countries.^[7] For example, in Turkey, the estimated prevalence rate of *H. pylori* infection is around 75.5%.^[8] Given the high prevalence and potentially serious clinical consequences of chronic *H. pylori* infection,

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the identification of highly effective and well-tolerated treatment regimens is important. However, despite significant improvements, attempts to achieve a simple 100% effective therapy for *H. pylori* have not yet been successful. Furthermore, although the “test and treat” approach is acceptable in high prevalence regions such as Turkey, resistance to antibiotics is an important problem and the eradication rate is decreasing worldwide.^[9] Therefore, clinically adequate regimens should provide *H. pylori* eradication in at least 80% of patients and should not cause any major adverse effects or clinically significant resistance to antibiotics. However, the most widely accepted standard triple therapy, consisting of amoxicillin, clarithromycin, and a proton pump inhibitor (PPI), has an eradication rate between 40% and 60%,^[10,11] and resistance to clarithromycin is considered the major reason for treatment failure. Consequently, new regimens are needed to achieve a higher eradication rate.

Recent management guidelines published by the Maastricht Consensus Conference and the American College of Gastroenterology recommend a combination of a PPI, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10–14 days and a combination of PPI, clarithromycin, and amoxicillin (clarithromycin triple therapy) for 7–14 days as first-line treatments for *H. pylori* infection.^[7,12]

Therefore, the aim of this study was to assess the efficacy and safety of a 7-day and a 14-day bismuth subsalicylate modified quadruple therapy (lansoprazole, amoxicillin, clarithromycin, and bismuth subsalicylate) for the eradication of *H. pylori*.

MATERIALS AND METHODS

Patient characteristics and study design

This prospective, open-label, single-center, randomized study was conducted in the Gastroenterology Clinic of Erciyes University. The study was performed between March 2011 and January 2012. The study included 70 consecutive patients (23 male, 47 female) who underwent endoscopy for functional dyspepsia and were found to have *H. pylori*. Patients were excluded if they were younger than 18 years, had a history of previous gastric surgery or *H. pylori* eradication treatment, had recently used bismuth-containing compounds or antibiotics (in the last 2 months) or PPI (in the last 2 weeks), had impaired liver or renal function, pyloric stenosis, erosive gastritis, or a peptic ulcer, had a history of allergies to penicillin or any other antibiotic, had used corticosteroids or immunosuppressants in the last 2 weeks, or were pregnant or lactating. The exclusion criteria also included a history of bleeding

and coagulation disorders or contraindication for biopsy sampling. Patient data were recorded using a questionnaire. A positive stool antigen test (SAT) was required for inclusion. This positive result was then confirmed by histology of the gastric mucosal biopsies prior to treatment. Patients with only one positive test were not eligible for enrolment.

Patients were randomized into two groups according to presenting order (1:1). Patients in group A ($n = 35$) received lansoprazole 30 mg twice daily (bid), amoxicillin 1000 mg bid, clarithromycin 500 mg bid, and bismuth subsalicylate 600 mg bid for 7 days (LACB-7). Patients in group B ($n = 35$) received the same therapy for 14 days (LACB-14). Figure 1 summarizes the patient distribution across the two treatment arms. Patients were asked about adverse effects throughout the treatment. Patient compliance was evaluated at the end of treatment by examining the pill count and was considered adequate if more than 80% of the medication had been taken. *H. pylori* eradication was considered successful if the SAT was negative 4 weeks after discontinuation of therapy. A positive SAT at week 4 suggested that treatment had failed and these patients were classified as non-eradicated.

Endoscopy and biopsy specimens

To carry out the histological evaluation, two antrum and one corpus biopsy specimens were obtained from each patient. Biopsies were fixed in formalin and routinely processed in paraffin wax. Consecutive 3- μ m sections were cut and stained with hematoxylin and eosin, as well as Giemsa, for the differential detection of *H. pylori*. All biopsy samples were examined by the same pathologist. *H. pylori* colonization and activity of gastritis were graded according to the updated Sydney system on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe).^[13]

Ethical approval

The study protocol was carried out in accordance with the Declaration of Helsinki (2004 revision). All subjects were informed about the study protocol and provided written consent. The study protocol was approved by the Erciyes University ethics committee.

Statistical analyses

The Shapiro–Wilk test was used to check the normality of the data. To compare the differences between groups, an independent-samples *t* test was used for continuous variables and a χ^2 analysis was used for categorical variables. The 95% confidence interval (CI) was calculated for categorical variables and the mean \pm standard deviation (SD) was used for quantitative variables. Data were expressed as frequencies and

percentages or mean ± SD. *P* values <0.05 were considered statistically significant. An analysis of covariance was used to assess the association between *H. pylori* status and functional dyspepsia status, adjusting for age and gender. Data were analyzed using SPSS v15 for Windows (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Of the 70 patients in the total sample, 47 (67.2%) were women and 23 (32.8%) were men. The mean age was 39.7 ± 11.2 years (38 ± 9.6 years for women and 42 ± 12.4 years for men). Of the 35 subjects in group A, 11 (31.4%) were men with a mean age of 50.3 ± 10.2 years and 24 (68.6%) were women with a mean age of 38.9 ± 11.1 years. Of the 35 subjects in group B, 12 (34.2%) were men with a mean age of 34.7 ± 9 and 23 (65.8%) were women with a mean age of 36.6 ± 7.6 years. Sixty-four patients completed the study. Of the six patients who did not complete the study (three

in group A and three in group B), four were lost to follow-up and two stopped treatment prematurely. The baseline characteristics of both groups are presented in Table 1. The per-protocol (PP) population consisted of 32 patients in the LACB-7 group and 32 patients in the LACB-14 group who completed their regimens.

The cumulative PP and intent-to-treat (ITT) eradication rates were 89% (*n* = 57/64) and 81.4% (*n* = 57/70) among the total sample, respectively. *H. pylori* eradication was achieved in 28 of 32 patients in the LACB-7 group (PP eradication: 87.5%; ITT eradication: 80%) and 29 of 32 patients in the LACB-14 group (PP eradication: 90.6%; ITT eradication: 82.8%). Both the PP and ITT eradication rates were superior in the LACB-14 group compared with the LACB-7 group, although the differences were not statistically significant after adjusting for age and sex (*P* = 0.689). All eradication rates, treatment differences, and 95% CIs are summarized in Table 2.

The treatment was well tolerated, no major adverse effects were reported, and no patients dropped out due to adverse events. The most common adverse effects were mild diarrhea and a metallic taste in the mouth. In response to direct questioning, dark stools were reported by more than 70% of the patients during treatment. All patients reported complete adherence to treatment. Only 13 patients (20.3%) presented minor-to-moderate adverse effects (six reported metallic taste, four mild diarrhea, and three occasional nausea). All adverse effects disappeared shortly after the end of treatment. The rate of adverse events did not differ significantly between the two groups [Table 3].

Table 1: Baseline demographic data

Characteristics	LACB-7	LACB-14
Number of patients	35	35
Mean age (SD) (years)	43 (11.8)	35.8 (8)
Male/female	11/24	12/23

LACB-7, lansoprazole/amoxicillin /clarithromycin/bismuth subsalicylate quadruple therapy for 7 days; LACB-14, lansoprazole/amoxicillin/clarithromycin/bismuth subsalicylate quadruple therapy for 14 days; SD, standard deviation.

Table 2: Rates of *H. pylori* eradication by two different treatment regimens

	LACB-7	LACB-14	<i>P</i>
ITT	28/35	29/35	0.759
(95% CI)	80%	82.8%	
PP	28/32	29/32	0.689
(95% CI)	87.5%	90.6%	

CI, confidence interval; PP, per protocol; ITT, intention-to-treat; LACB-7, lansoprazole/amoxicillin /clarithromycin/bismuth subsalicylate quadruple therapy for 7 days; LACB-14, lansoprazole/amoxicillin/clarithromycin/bismuth subsalicylate quadruple therapy for 14 days.

Table 3: The incidence of mild-to-moderate adverse effects in each group

Adverse effects	LACB-7	LACB-14
Nausea/vomiting	1	2
Alteration of taste	2	4
Diarrhea	2	2
Total	5	8

LACB-7, lansoprazole/amoxicillin /clarithromycin/bismuth subsalicylate quadruple therapy for 7 days; LACB-14, lansoprazole/amoxicillin/clarithromycin/bismuth subsalicylate quadruple therapy for 14 days;

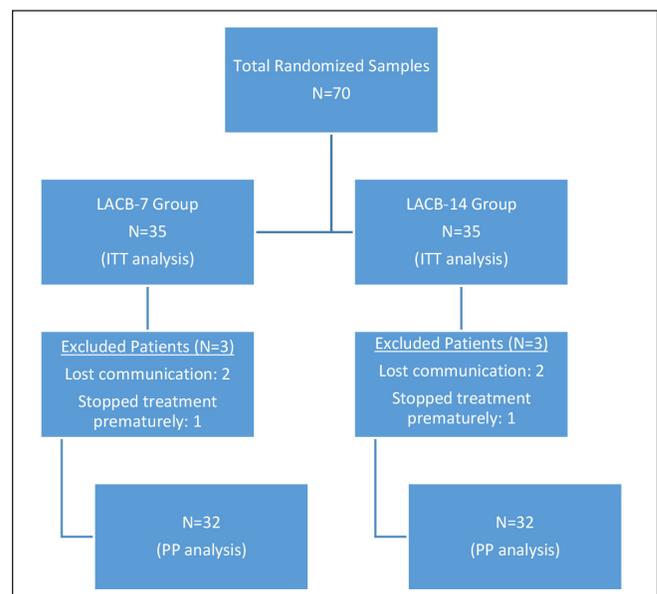


Figure 1: Patient distribution flowchart

DISCUSSION

H. pylori eradication leads to histologic and endoscopic improvement for several conditions. For example, *H. pylori* eradication has been shown to result in regression of mucosa-associated lymphoid tissue (MALT) lymphoma in 60–80% of *H. pylori*-positive patients with gastric MALT lymphoma.^[14] Therefore, *H. pylori* eradication therapy should be the first choice of treatment. In addition, compared with conventional therapy, *H. pylori* eradication therapy has been shown to inhibit recurrence and provide economic benefits.^[15] Furthermore, in a large-scale, multicenter, Japanese study, patients who had received endoscopic treatment for early gastric cancer and who were randomized to the *H. pylori* eradication group showed a markedly lower rate of metachronous recurrence after 3 years when compared with the non-eradication group.^[16] These findings show that *H. pylori* eradication can inhibit the development of gastric cancer. Thus, the consensus among international guidelines is that unless a patient is allergic to any of the drugs used in eradication therapy or has complications that could interfere with eradication, such therapy should be the first-line treatment for an *H. pylori*-positive peptic ulcer.^[17]

However, antibiotic resistance to clarithromycin has been identified as one of the major factors affecting our ability to cure *H. pylori* infection. Clarithromycin resistance is caused by mutations of *H. pylori* 23S ribosomal RNA inside 50S ribosomal subunits. These mutations result in decreased binding of clarithromycin to *H. pylori* ribosomes thereby reducing or preventing inhibition of protein expression.^[18] In addition, the rate of resistance to this antibiotic seems to be increasing in many areas.^[19] For example, in Turkey, while the rate of resistance to clarithromycin was 18.7% in 2000, in 2009 it had increased to 41.9%.^[20,21] Furthermore, in a large randomized study performed in our country, the eradication rate of standard triple therapy (omeprazole, clarithromycin, and amoxicillin) for 14 days was found to be 43%.^[22] A meta-analysis by Kadayifçi *et al.*^[10] revealed that the *H. pylori* eradication rate of PPI-based triple therapy regimens was 84% in 1997, but decreased to 55.3% in 2004. These results emphasize the importance of investigating alternative treatments, such as bismuth-based treatments, for eradication of *H. pylori*.

Bismuth is an established treatment for *H. pylori*,^[23] as it exerts a direct bactericidal effect on *H. pylori*, and to date, no resistance to bismuth salts has been reported.^[24] Bismuth has already been proposed as a first-line eradication regimen because of its eradication rate approaching 90%,^[25] synergistic effects with

metronidazole and clarithromycin, and lack of *H. pylori* resistance.^[26] Thus, bismuth-based quadruple therapy has reemerged and is currently considered the preferred regimen in areas where clarithromycin resistance is high.

Furthermore, some studies have shown that prolonging the duration of therapy might improve the success of treatment. For example, a previous meta-analysis has shown that extending the duration of clarithromycin-based treatment from 7 days to 14 days led to a 12% higher eradication rate,^[27] and a comparison between a 5-day and a 7-day clarithromycin-based triple therapy (lansoprazole 30 mg bid, amoxicillin 500 mg bid, and clarithromycin 200 mg bid) for non-resistant *H. pylori* infection showed a significantly higher eradication rate with the 7-day regimen [93% ($n = 39/42$) versus 75% ($n = 36/84$), respectively].^[28] Similarly, our results showed that 14 days of treatment with LACB therapy yielded higher *H. pylori* eradication rates than 7 days of treatment, supporting this hypothesis. However, there was no statistically significant difference between the two groups. Nonetheless, the findings of this study have important implications for the treatment of *H. pylori* infection given that both LACB regimens were superior to standard lansoprazole, amoxicillin, and clarithromycin protocols.

Although the results of our study are novel and interesting, our study does have some limitations. First, because isolation of *H. pylori* is expensive, we were not able to evaluate antibiotic resistance in relation to treatment regimens or eradication rates. Secondly, the number of patients in each group was relatively small.

CONCLUSIONS

Both the 7-day and 14-day bismuth subsalicylate-containing first-line quadruple therapies were safe and effective against *H. pylori*. Both therapies provided a high cure rate ($\geq 80\%$), were well tolerated and were equally effective against *H. pylori* infection in Turkey. Although previous studies have evaluated an LACB regimen as a second-line *H. pylori* treatment, to the best of our knowledge, our study is the first to evaluate 7-day and 14-day bismuth subsalicylate-containing quadruple therapy regimens as first-line eradication therapies in Turkey. In regions with high levels of clarithromycin resistance, treatment with a modified LACB therapy should be considered as first-line therapy for *H. pylori* eradication.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Malaty HM. Epidemiology of *Helicobacter pylori* infection. *Best Pract Res Clin Gastroenterol* 2007;21:205-14.
- Eslick GD, Lim LL, Byles JE, Xia HH, Talley NJ. Association of *Helicobacter pylori* infection with gastric carcinoma: A meta-analysis. *Am J Gastroenterol* 1999;94:2373-9.
- El-Omar EM, Penman ID, Adrill JES, Chittajallu RS, Howie C, McColl KE. *Helicobacter pylori* infection and abnormalities of acid secretion in patients with duodenal ulcer disease. *Gastroenterology* 1995;109:681-91.
- Franchini M, Cruciani MM, Mengoli C, Pizzolo G, Veneri D. Effect of *Helicobacter pylori* eradication on platelet count in idiopathic thrombocytopenic purpura: A systematic review and meta-analysis. *J Antimicrob Chemother* 2007;60:237-46.
- Choe YH, Kim SK, Son BK, Lee DH, Hong YC, Pai SH. Randomized placebo-controlled trial of *Helicobacter pylori* eradication for iron-deficiency anemia in preadolescent children and adolescents. *Helicobacter* 1999;4:135-9.
- Malfërtheiner P, Megraud F, O'Morain CA, Atherton J, Axon ATR, Bazzoli F, *et al.* Management of *Helicobacter pylori* infection-The Maastricht IV/Florence Consensus Report. *Gut* 2012;61:646-64.
- Suerbaum S, Michetti P. *Helicobacter pylori* infection. *N Engl J Med* 2002;347:1175-86.
- Akın L, Tezcan S, Haşçelik G, Cakir B. Seroprevalence and some correlates of *Helicobacter pylori* at adult ages in Gülveren Health District, Ankara, Turkey. *Epidemiol Infect* 2004;132:847-56.
- Kearney DJ. Retreatment of *Helicobacter pylori* infection after initial treatment failure. *Am J Gastroenterol* 2001;96:1335-9.
- Kadayifçi A, Büyükhatoğlu H, Koruk M. Efficacy of a proton pump inhibitor plus amoxicillin plus clarithromycin in the eradication of *H. pylori* in Turkey: A meta-analysis. *Turk J Gastroenterol* 2004;15 (Suppl 1):5.
- Gülter S, Keleş H, Ozkurt ZN, Cengiz DU, Kolukisa E. Can lansoprazole, amoxicillin, and clarithromycin combination still be used as a first-line therapy for eradication of *Helicobacter pylori*. *Turk J Gastroenterol* 2005;16:29-33.
- Chey WD, Wong BC. Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol* 2007;102:1808-25.
- Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston. 1994. *Am J Surg Pathol* 1996;20:1161-81.
- Bayedorffer E, Neubauer A, Rudolph B, Thiede C, Lehn N, Eidt S, *et al.* Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue type after cure of *Helicobacter pylori* infection. MALT Lymphoma Study Group. *Lancet* 1995;345:1591-4.
- Ford AC, Delaney BC, Forman D, Moayyedi P. Eradication therapy in *Helicobacter pylori* positive peptic ulcer disease: Systematic review and economic analysis. *Am J Gastroenterol* 2004;99:1833-55.
- Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, *et al.* Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: An open-label, randomised controlled trial. *Lancet* 2008;372:392-7.
- Asaka M, Kato M, Takahashi S, Fukuda Y, Sugiyama T, Ota H, *et al.* Guidelines for the management of *Helicobacter pylori* infection in Japan: 2009 Revised Edition. *Helicobacter* 2010;15:1-20.
- Taylor DE, Ge Z, Purych D, Lo T, Hiratsuka K. Cloning and sequence analysis of two copies of a 23S rRNA gene from *Helicobacter pylori* and association of clarithromycin resistance with 23S rRNA mutations. *Antimicrob Agents Chemother* 1997;41:2621-8.
- Megraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, *et al.* *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013;62:34-42.
- Göral V, Zeyrek FY, Gül K. Antibiotic resistance in *Helicobacter pylori* infection. *T Klin Gastroenterohepatol* 2000;11:87-92.
- Bakir Ozbey S, Ozakin C, Keskin M. Antibiotic resistance rates of *Helicobacter pylori* isolates and the comparison of E-test and fluorescent in situ hybridization methods for the detection of clarithromycin resistant strains. *Mikrobiyol Bul* 2009;43:227-34.
- Gumurdulu Y, Serin E, Ozer B, Kayaselcuk F, Ozsahin K, Cosar AM, *et al.* Low eradication rate of *Helicobacter pylori* with triple 7-14 days and quadruple therapy in Turkey. *World J Gastroenterol* 2004;10:668-71.
- Ford AC, Malfërtheiner P, Giguere M, Santana J, Khan M, Moayyedi P. Adverse events with bismuth salts for *Helicobacter pylori* eradication: Systematic review and meta-analysis. *World J Gastroenterol* 2008;14:7361-70.
- Dore MP, Graham DY, Mele R, Marras L, Nieddu S, Manca A, *et al.* Colloidal bismuth subcitrate-based twice-a-day quadruple therapy as primary or salvage therapy for *Helicobacter pylori* infection. *Am J Gastroenterol* 2002;97:857-60.
- Veldhuyzen Van Zanten S, Farley A, Marcon N, Lahaie R, Archambault A, Hunt R, *et al.* Bismuth-based triple therapy with bismuth subcitrate, metronidazole and tetracycline in the eradication of *Helicobacter pylori*: A randomized, placebo controlled, double-blind study. *Can J Gastroenterol* 2000;14:599-602.
- Lambert JR, Midolo P. The actions of bismuth in the treatment of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 1997;11 (Suppl 1):27-33.
- Calvet X, Garcia N, Lopez T, Gisbert JP, Gene E, Roque M. A meta-analysis of short versus long therapy with a proton pump inhibitor, clarithromycin and either metronidazole or amoxicillin for treating *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2000;14:603-9.
- Ogura K, Yoshida H, Maeda S, Yamaji Y, Kawabe T, Okamoto M, *et al.* Clarithromycin-based triple therapy for non-resistant *Helicobacter pylori* infection. How long should it be given. *Scand J Gastroenterol* 2001;36:584-8.