



First-Line Treatment in the Eradication of *Helicobacter Pylori*: where are we now?



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Abstract

Aim: *Helicobacter pylori* (HP) are the most common human infectious agent worldwide. Approximately half of the patients remain infected after 'eradication' treatment with the triple regimen of a proton pump inhibitor (PPI), amoxicillin (AMO), and clarithromycin (CLA). In this study, this PPI-based triple regimen was compared to a quadruple regimen, including bismuth citrate (BC), a PPI, metronidazole (MET), and tetracycline (TET), and BPMT.

Methods: Total 215 patients who were treated with lansoprazole (LAN), AMO and CLA (LAC); and another 210 patients who were treated with BPMT for 14 days for the purpose of HP eradication between January 2011 and April 2014 were included in this study. The treatment period was 14 days for both groups.

Results: Demographic characteristics and endoscopic findings were similar in both groups. The HP eradication rate was % 53.4 in the LAC group, and it was %78.5 in the BPMT group ($P < 0.05$). The rates of non-compliance with treatment and side effects were higher in the BPMT group ($P < 0.05$). Among all, 55 patients in the LAC group and 110 patients in the BPMT group were reported to have had difficulties conforming to the treatment ($P = 0.020$). In the questionnaire on the side effects of the drugs, 30 patients in the LAC group and 90 in the BPMT group gave positive answers ($P = 0.006$). The most frequently reported side effects were dry mouth and metallic taste. The eradication rates were % 53.4 in the LAC regimen, and %78.5 in the BPMT regimen. This difference was statistically significant ($P = 0.026$).

Conclusion: The efficacy of LAC for HP eradication in Turkey has diminished due to high microbial resistance to antibiotics. The BPMT regimen should be considered a first-line treatment because of its higher eradication rate. We suggest that BPMT could be accepted as a first-line treatment for acute HP infection. LAC is an alternative treatment for a select group of patients.

Keywords: *Helicobacter pylori*; Eradication; Triple regimen; Quadruple regimen

Introduction

Helicobacter pylori (HP) are the most common human infectious agent worldwide [1]. In some countries the prevalence is up to 85-90% [2]. It plays a role in the aetiology of many gastric disorders including adenocarcinoma, and is associated with some haematological, neurological, and cardiovascular conditions [3-7]. Since the discovery of HP, the triple regimen treatment has been used as the standard approach for its eradication. This consists of a PPI and two antibiotics, usually AMO and CLA [1,5,7-29]. In recent years other antibiotics have also been used [30,31]. Because of the development of microbial resistance to CLA worldwide, more attention has been paid to alternative therapies. Thus, a BC-containing quadruple regime has been

widely used in recent years [1,4,5,7,15,17,19,21,25,27,32-40]. Recent studies carried out in our country have indicated that microbial resistance to CLA has risen beyond %50, rendering the success of the classical triple regimen unacceptably poor [3,16,20,26,28,41,42].

Given all of these studies, alternatives to the standard PPI regimen have drawn the attention of clinicians. In our clinic, HP eradication treatment now consists of a 14-day course of oral tablets, consisting of a BC 600 mg tablet BID, a PPI (OME 200 mg or LAN 30 mg) capsule BID, an MET 500 mg tablet TID, and a TET 500 mg tablet QID. This is the quadruple BPMT regimen. Our previous approach used to be the triple regimen of a LAN

30 mg capsule BID, an AMO 1000 mg tablet BID, and a CLA 500 mg tablet BID. In the present study, we compared these two commonly applied first-line treatments to the eradication of HP.

In our country, there are endoscopy units in most general surgery hospitals. HP is the most common infection throughout the world and has been shown to be associated with gastric cancer. Thus, data concerning HP eradication are a matter of concern not only for medical gastroenterologists but also for general surgeons.

Patients and Methods

Total 425 patients who underwent endoscopic biopsies and were found to have HP infection received 14-day treatments for HP eradication. Following the treatment, a second endoscopy and a urea breath test (Heliprobe, Noster AB, Sweden) or an HP stool antigen test (Antigen card test, Dialab, Austria) were done to evaluate the rate of eradication. The patients were divided into two groups: group I (LAC) and group II (BPMT). The patients were randomised into LAC and BPMT groups with a computer-generated random number. The patients were evaluated for eradication rate, difficulty in conforming to the treatment, and drug side effects. Smoking habits, alcohol consumption, and use of other drugs were also recorded. Reports of pathological examinations were scrutinised for the presence of precancerous lesions and these results were also recorded. All study participants, or their legal guardian, provided written informed consent prior to study enrolment.

Statistical Analysis

The SPSS software (ver. 15.0; SPSS Inc., Chicago, IL, USA) was used to analyse the data. The χ^2 test was used for comparisons. P values < 0.05 were considered to indicate statistical significance.

Results

There were 215 patients in the 'classical' LAC group and 210 in the BPMT group. Patient demographic characteristics, co-morbidities, smoking habits, alcohol consumption habits, and use of other drugs were similar between the groups (P > 0.05) (Table 1). There were also no significant differences between the groups in terms of endoscopic biopsy findings (P > 0.05) (Table 2).

Table 1: Patients characteristics according to their groups.

	LAC (n = 213)	BPMT (n = 210)	P-Value
Age: mean (range) years	48.2 (25-80)	43.5 (18-75)	
Gender: (M/F)	100/115 (M: 46.5%)	100/110 (M: 47.6%)	0.917
Co-morbidities	75 (34.8%)	65 (30.9%)	0.621
Smoking habits	55 (25.5%)	50 (23.8%)	0.776
Alcohol consumption	20 (9.3%)	15(71%)	0.616
Other drug use	105 (48.8%)	90 (42.8%)	

-NSAID	40	35	
-Anti hypertensive	30	25	
-Anti diabetics	25	25	
-Anti depressants	10	5	0.531

LAC: lansoprazole, amoxicillin, and clarithromycin triple regimen, BPMT: bismuth citrate, proton pump inhibitor, metronidazole, and tetracycline quadruple regimen, M: male, F: female, NSAID: non-steroidal anti-inflammatory drug.

Table 2: Endoscopic biopsy findings in the groups.

Endoscopic Biopsy Findings (HP Gastritis and Ulcers)	LAC	BPMT	P-value
Intestinal metaplasia	40	40	1
Tubular/tubulovillous adenoma	10	5	0.256
Oedematous gastric mucosa	5	10	0.256
Gastric dysplasia	0	5	0.563
Carcinoid tumour	0	5	0.563

HP: Helicobacter Pylori; LAC: Lansoprazole Amoxicillin and Clarithromycin Triple Regimen; BPMT: Bismuth Citrate Proton Pump Inhibitor Metronidazole and Tetracycline Quadruple Regimen

In all, 55 patients in group 1 and 110 patients in group II reported difficulties in conforming to the treatments (P = 0.020). In the questionnaire for drug side effects, 30 patients in group I and 90 in group II reported positive answers (P = 0.006). The most frequently reported side effects were dry mouth and metallic taste. Evaluating eradication rates, the LAC regimen was % 53.4successful and the BPMT regimen was %78.5 successful. This difference was statistically significant (P = 0.026) (Table 3).

Table 3: Rates of difficulties in conforming to treatment, side effects and eradication in the groups.

	LAC	BPMT	P-value
Difficulty in conforming with treatment	55 (25.5%)	110 (52.3%)	0.02
Side effects	30 (13.9%)	90 (42.8%)	
-Dry mouth	10	30	0.006
-Metallic taste	15	25	0.006
-Abdominal pain	5	15	
-Nausea vomiting	0	20	0.026
Eradication	115 (53.4%)	165 (78.5%)	

LAC: Lansoprazole Amoxicillin and Clarithromycin Triple Regimen; BPMT: Bismuth Citrate Proton Pump Inhibitor Metronidazole and Tetracycline Quadruple Regimen.

Discussion

HP is a Gram-negative spiral bacteria and the most common infectious agent worldwide. It is estimated that about half of the global population is infected. It is an important factor in the aetiology of gastritis, gastric and duodenal ulcers, gastric mucosa-associated lymphoma (MALT), and gastric adenocarcinoma [3-6].

Recent studies have shown that HP infection is also associated with some diseases outside the gastrointestinal system, including refractory iron deficiency anaemia, idiopathic thrombocytopenic purpura (haematological system) paralysis, Parkinson's disease, Alzheimer's disease (neurological system), and ischemic heart disease (cardiovascular system) [7].

Since the discovery of HP in 1983, diagnostic and therapeutic approaches to gastritis and peptic ulcers have changed greatly [29]. In 1994, the World Health Organization International Agency for Research on Cancer reached the conclusion that HP has a causative relationship with gastric carcinogenesis and that the agent is a definite carcinogen in humans [43]. Since then, much more attention has been focused on this agent. In the Mongolian gerbil model, it was shown that HP could induce gastric cancer independent of exposure to low-dose chemical carcinogens [44]. In the early 2000s, survey studies carried out in Japan showed that HP infection increased the risks of intestinal metaplasia and diffuse-type gastric cancer [29,45]. The estimated risk of developing cancer attributable to HP varies between 50% and 73% [46]. In a randomised study carried out in Colombia that included patients with high-risk and precancerous lesions, it was observed that there was a significant decrease in cancer rate among those who had HP eradicated [46]. In another randomised study carried out in China, HP eradication significantly decreased the risk of gastric cancer in individuals without gastric atrophy and intestinal metaplasia or dysplasia [47]. The benefit of HP eradication on gastric cancer has been a subject in other studies too. A study in Japan showed that gastric cancer risk in the residual stomach after distal gastrectomy and Billroth I anastomosis for previous gastric cancer decreased significantly subsequent to HP eradication [48].

Currently, various treatment protocols are being used for the eradication of HP. It was reported that prior to the 2000s, the triple regimen was successful at a rate of ~95% [18]. However, with the development of microbial resistance to CLA, this success rate has decreased to 55-22%. Thus, there has recently been a trend towards the quadruple regimen including BC, which has anti-HP and mucosal cytoprotective effects. For this reason, it is expected that protocols including BC will be effective [49]. Indeed, some studies have shown this regimen to be effective [5,13].

In this study, we compared the most commonly used first-line treatment protocols. The choice of OME or LAN as the PPI in BPMT depends on the clinician's preference. However, a previous study reported no significant differences between various PPIs in terms of efficacy [50]. In the present study, a second endoscopic examination, and a urea breath test or HP stool antigen test was done at least 8 weeks after treatment to evaluate the rate of eradication. Other studies have shown that these tests have the same value and their sensitivities and specificities exceed 90% [51-54]. The use of different PPI drugs did not seem to have affected our results.

There were no significant differences between our patient groups in terms of their general characteristics and endoscopic biopsy findings. However, the rate of difficulty in conforming to treatment and side effects were higher in the BPMT group. This could be due the high number of tablets prescribed (13 tablets daily) and the high doses. Indeed, other studies have also referred to difficulties in the use of the BPMT protocol [3]. Patients are advised to take the drugs after meals and to drink a lot of water to minimise the side effects of the antibiotics. Other studies have proposed the use of probiotics to minimise the side effects of antibiotics and increase eradication [7,15].

Evaluation of the eradication rates in our study showed a 78.5% success rate in the BPMT group and 53.4% success in the LAC group.

This difference was statistically significant. The low success rate in the LAC group is consistent with the results of other studies carried out in our country and is attributed to increased microbial resistance to CLA [16,20,42]. A meta-analysis in our country showed that the success rate of the triple regimen was 79.4% in 1996 and decreased to 61.1% in 2005 [26]. In recent years, this rate has been estimated to be 50-55% [20]. Although the success rate with BPMT was higher (78.5%) than that with LAC, this rate was well below expectations. The reason for this could be the growing resistance to MET in our country and worldwide [3,7,22].

Other treatment approaches should be considered for cases where eradication is unsuccessful. Currently, various alternative regimens are being used. These include successive, combination, hybrid, and rescue regimens, some of which include the use of levofloxacin and the classical anti-tuberculosis agent rifabutin [7,15]. Limitations of our study included patient's not completing follow-up, reporting too late for re-evaluation, and insufficient information being obtained from the patients.

Conclusion

A 14-day treatment with the BPMT regimen was more successful than the classical LAC regimen for HP eradication. In some patients, drug side effects and difficulty conforming to the treatment were a problem. In cases of unsuccessful eradication, other regimens described in the literature should also be considered.

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