

Appropriateness of *Helicobacter pylori* eradication therapy in gastroenterology patients of a tertiary care hospital

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ABSTRACT

Recommended and widely used first-line treatment of *Helicobacter pylori* consists of a proton pump inhibitor, clarithromycin, and amoxicillin/metronidazole. Recent reports suggest an increase in resistance to these antibiotics, especially to clarithromycin which has adversely affected the effectiveness of this standard regimen, hence levofloxacin containing regimens have also been introduced. Our objective was to assess the appropriateness of clarithromycin and levofloxacin containing regimens for *H. pylori* eradication by considering the factors such as dose, duration of treatment, patient medication adherence, and *H. pylori* induced symptom relief. In this prospective observational study, 120 patients were enrolled on the basis of *H. pylori* induced symptoms, positive campylobacter-like organism (CLO) test, or histology proven *H. pylori* infection. Besides socio-demographic characteristics, endoscopic findings, CLO test results and *H. pylori* induced symptom eradication were documented. Majority of the patients (85.83%) received an eradication regimen consisting of clarithromycin + amoxicillin + pantoprazole and the remaining patients were prescribed levofloxacin containing regimens. *H. pylori* eradication regimen containing clarithromycin was more effective in symptom control. Based on both symptom relief and a negative CLO test on treatment completion, only 40% of the patients received benefit from the regimens. Moreover, overall therapy was unsatisfactory due to inappropriate dose, duration, or sub-optimal adherence.

INTRODUCTION

Helicobacter pylori is a microaerophilic, spiral-shaped, gram-negative bacterium with several flagella for motility. It can grow only at a periplasmic pH of 6.0–8.5 though it can stay alive at a pH of 4.0. One of the known biochemical properties of *H. pylori* is its capability to produce urease, which can hydrolyze gastric urea to release ammonia, and raise the periplasmic pH to 4.0–6.0 and thereby protecting the organism from gastric acidity (Marshall *et al.*, 1985). *Helicobacter pylori* infection is common worldwide and can result in acute or chronic gastritis, peptic ulcer disease, and can also cause mucosa-associated tissue lymphoma. Additionally, *H. pylori* seems to be associated with functional dyspepsia

(Chey *et al.*, 2017, Viswanathan *et al.*, 2018). The diagnostic tests for *H. pylori* include both invasive (culture and sensitivity analysis, histology, and rapid urease test) and non-invasive tests (urea breath test, stool antigen test, and serology). Rapid urease test, also known as campylobacter-like organism (CLO) test, is simple and less time-consuming and has a sensitivity of 95% and specificity of 80%–90% while histology test has a sensitivity of 60%–90% and specificity >95% but neither of them gives any data about antibiotic resistance of the organism (Songur *et al.*, 1995).

Recommended and widely used first-line treatment of *H. pylori* consists of a combination of a proton pump inhibitor (PPI), clarithromycin, and amoxicillin/metronidazole (Chey *et al.*, 2017). PPIs raise the gastric pH and thereby the organism is kept in an active state of cell division which will enable the killing of the bacteria by the antibiotics (Scott *et al.*, 1998). Since the organism is relatively resistant to antibiotics, combinations of antibiotics are necessary. The timing of administration of drugs is also important to obtain a maximum

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therapeutic response, normally anti-secretory agents should be taken half an hour before food (Hatlebakk *et al.*, 2000) and giving antibiotics after meals improves their intra-gastric distribution and prolongs their gastric residence time. However, the timing of antibiotic administration in relation to meals is not so important in *H. pylori* eradication therapy (Atherton *et al.*, 1994). Medication adherence is the most important factor in *H. pylori* eradication. Poor adherence to therapy is associated with significantly lower levels of eradication. Factors influencing adherence include the complexity and duration of treatment. The opportunity to improve medication adherence exists at every point of contact between the patient and the medical services (Anthony O'Connor *et al.*, 2009).

However, recent reports note a rise in the incidence of resistance to the antibiotics, especially clarithromycin which has adversely affected the effectiveness of the standard regimen (Papastergiou *et al.*, 2014). Levofloxacin regimen consisting of levofloxacin + amoxicillin + pantoprazole was prescribed as a salvage or alternative regimen for *H. pylori* eradication (Myran and Zarbock, 2018). In areas of high clarithromycin resistance, levofloxacin-based and sequential therapy were superior to standard triple therapy as first-line regimens (Molina-Infante *et al.*, 2010). A clinical trial has shown that the triple therapy regimen containing levofloxacin was better than quadruple therapy (Bilardi *et al.*, 2004). The success rate of 70% observed with such a triple therapy indicates that a 10 day treatment of pantoprazole, amoxicillin, and levofloxacin should be considered in patients who had failed one or more of the other eradication regimens. But a study from Bangladesh showed that the rate of resistance to clarithromycin, metronidazole, and levofloxacin was high in Bangladesh suggesting that triple therapy-based regimen may not be useful as first-line therapy (Aftab *et al.*, 2016).

A study from Gujarat, India showed that *H. pylori* resistance to metronidazole was 83.8% and that to clarithromycin and amoxicillin was 58.8% and 72.5%, respectively (Pandya *et al.*, 2014). A recent study from Karnataka, India reported high resistance to metronidazole (81.4%) and levofloxacin (54.9%) and modest resistance (20.4%) to clarithromycin in *H. pylori* strains. Multidrug resistance was shown in 59.3% of total strains, in which 86.6% were resistant to at least both metronidazole and levofloxacin (Shetty *et al.*, 2019). Because of the rising frequency of antimicrobial resistance, the management of *H. pylori* infections is a challenge for physicians. The most effective drug was rifabutin and the lowest sensitive drug was metronidazole in an earlier report (Kwon *et al.*, 2001). Worldwide, *H. pylori* resistance to clarithromycin and levofloxacin has increased during the last 6 years. Many reports of resistance to antimicrobial agents describe a dramatic decrease in the efficacy of antibiotics (Baubie *et al.*, 2019; Gisbert *et al.*, 2015).

Besides antibiotic resistance, the success of *H. pylori* treatment depends on other factors such as the dose of the antimicrobial drugs, the duration of therapy and patient's medication adherence. In this study, we aimed to assess the appropriateness of various *H. pylori* eradication regimens in gastroenterology patients of a tertiary care hospital by considering the factors such as dose, duration, patient's medication adherence, and *H. pylori* induced symptom eradication after treatment completion.

MATERIALS AND METHODS

Patient selection

A total of 176 dyspeptic patients (96 males and 80 females) attending the gastroenterology department of Amrita Institute of Medical Sciences and Research Center (AIMS), Kochi, and receiving an *H. pylori* eradication regimen were screened for confirmation of *H. pylori* infection. A prospective observational follow-up study was then conducted on all the 120 patients who satisfied the inclusion and exclusion criteria (Fig. 1).

Inclusion criteria

Patients satisfying all the following criteria were included in the study

- Patients undergoing upper endoscopy due to dyspeptic symptoms
- Patients aged 18 to 70 years and treatment-naive for *H. pylori* eradication
- CLO test positive patients or patients whose antral biopsy showing the presence of *H. pylori*

Exclusion criteria

Patients with any of the following criteria were excluded from the study

- Patients who had received proton pump inhibitors, H2 receptor antagonists, bismuth salts, or antibiotics during the 4 weeks prior to study enrollment.
- Patients with malignant tumors of the digestive system
- Patients who had undergone gastrointestinal tract surgery
- Patients whose conditions were complicated by severe heart, lung, blood, liver, or kidney dysfunction
- Patients without informed signed consent

Choice of a particular regimen was at the discretion of treating physicians. The study was conducted from September 2018 to February 2019 after receiving approval by the Institutional Ethics Committee of AIMS (IEC-AIMS-2018-PHARM-31 dated 31/08/2018) and informed signed consent was obtained from all the patients enrolled.

After obtaining socio-demographic and medication history details of the patients, endoscopic findings, CLO test results, histology results of CLO test negative patients, and type of *H. pylori* eradication regimen given were recorded. All the eradication regimens were given on a twice daily basis. The medication adherence of the patients towards *H. pylori* eradication regimens was determined using a medication adherence reporting scale (Lee *et al.*, 2017). Endoscopic findings, CLO test results, and *H. pylori* induced symptoms [dyspepsia, gastro-esophageal reflux disease (GERD), and gastrointestinal (GI) blood loss] after completion of treatment were documented for patients in whom the CLO test was repeated. For all other patients, *H. pylori* induced symptoms (dyspepsia, GERD, and GI blood loss) after completion of treatment were noted. The absence of gastrointestinal symptoms and a negative CLO test on completion of therapy were the end points considered for the effectiveness of the regimens.

Statistical analysis

Statistical analysis was performed using IBM statistical package for the social sciences version 20.0 software. Categorical variables were expressed using frequency and percentage. Numerical variables were presented using mean and standard deviation. The effectiveness of different antibiotic regimens was compared, by the chi-square test. A *p* value of <0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

Our study (Fig. 2) shows that the most commonly prescribed antibiotic regimen for *H. pylori* eradication was HP pantocid kit[®] and most of the patients received it as a first-line therapy. HP pantocid kit[®] consists of a fixed-dose combination of clarithromycin 500 mg + amoxicillin 750 mg + pantoprazole 40 mg. American College of Gastroenterology (ACG) clinical

guidelines recommend the combination of clarithromycin 500 mg + amoxicillin 1 gm + pantoprazole 40 mg, but the dose of amoxicillin in HP pantocid kit[®] is suboptimal compared to that recommended in the ACG clinical guidelines (Chey *et al.*, 2017). Nexium HP7[®], another fixed dose combination pack of clarithromycin, amoxicillin, and esomeprazole for *H. pylori* eradication, has an amoxicillin content of 1 gm instead of 750 mg. The guidelines also recommend that the duration of therapy is 14 days, but in our study, 20% of the patients received HP pantocid kit[®] only for 10 days, followed by 5% receiving it only for 7 days. Hence, 25% (30/120) of our study patients received HP pantocid kit[®] for an inappropriate duration.

Second-line treatment prescribed for *H. pylori* eradication in our study was regimens containing levofloxacin, which were prescribed for 14.17% (17/120) of the patients. According to ACG clinical guidelines, levofloxacin regimen (levofloxacin 250 mg + amoxicillin 1 gm + pantoprazole 40 mg twice daily) should be prescribed for 10–14 days (Chey *et al.*, 2017). This regimen was prescribed appropriately for the patients (10/120, 8.33%) but 3.33% (4/120) of patients received a regimen of levofloxacin 500 mg + metronidazole 500 mg + pantoprazole 40 mg twice daily, which is not recommended by the ACG (Chey *et al.*, 2017). Other levofloxacin regimens received by the patients were levofloxacin 500 mg + amoxicillin 1 g + pantoprazole 40 mg × bis in die (BD) for 14 days, (levofloxacin 1,000 mg + amoxicillin 250 mg + pantoprazole 40 mg) × BD for 10 days, and (levofloxacin 250 mg + amoxicillin 500 mg + pantoprazole 40 mg) × BD for 14 days. But only one patient (0.83%, 1/120) each received these regimens. These regimens are also not recommended in the ACG clinical guidelines. A study from Karnataka showed high resistance to metronidazole and levofloxacin and modest clarithromycin resistance in *H. pylori* strains. Due to this metronidazole, levofloxacin and clarithromycin-based triple therapies are not suitable as first-line treatment in Karnataka, while amoxicillin and tetracycline can be used to eradicate *H. pylori* infection in that region (Shetty *et al.*, 2019). Bismuth containing regimen (bismuth subsalicylate 300 mg + tetracycline 500 mg + metronidazole 250–500 mg + PPI for 10–14 days, PPI twice daily and all other drugs four times daily) was not prescribed to any of our patients. This may be due to the high cost and non-availability of bismuth salts. Bismuth containing regimens is also endorsed by ACG for *H. pylori* eradication therapy in cases of resistance to clarithromycin.

Endoscopic findings of the study patients are shown in Figure 3. Some patients had more than one finding. Eighty patients were confirmed to have infection by positive CLO test and 40 patients had histologically proven *H. pylori* infection (Fig. 1). Based on *H. pylori* induced symptom eradication, antibiotic regimens prescribed were effective in 59.16% (71/120) of our study patients (Table 1). Of the patients who received HP pantocid kit[®] for 14 days, 83.56% (61/73) were adherent to the prescribed regimen but 57.5% (42/73) had no relief of symptoms (Fig. 4). Thus, the therapeutic response was not satisfactory for most of the patients, this may be related to the inappropriate dose of amoxicillin in HP pantocid kit[®] or prior exposure to macrolides leading to clarithromycin resistance. In such situations, bismuth quadruple therapy consisting of a PPI, bismuth, tetracycline, and

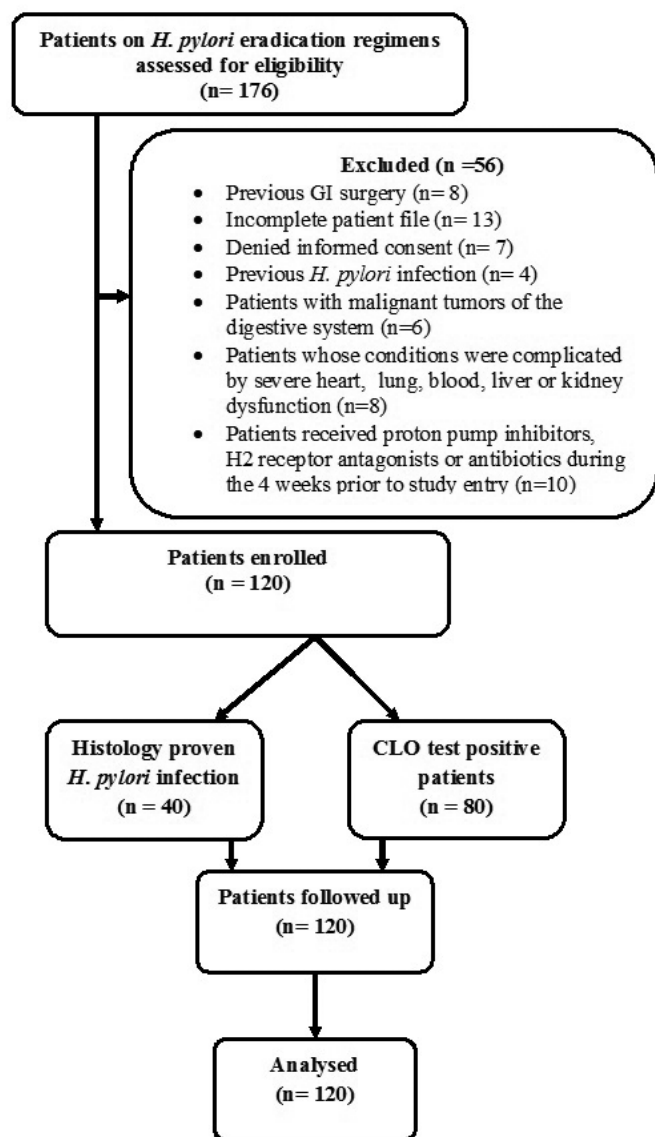


Figure 1. Flow chart of the study process.

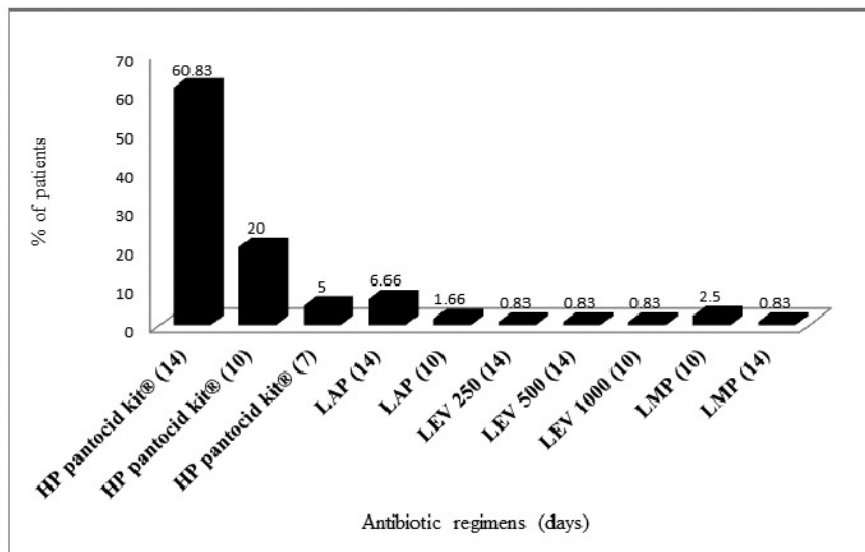


Figure 2. Prescribing pattern of *H. pylori* eradication regimens in the study patients. HP pantocid kit® = clarithromycin 500 mg + amoxicillin 750 mg + pantoprazole 40 mg, L.A.P = levofloxacin 250 mg + amoxicillin 1 g + pantoprazole 40 mg, LEV 250 = levofloxacin 250 mg + amoxicillin 500 + pantoprazole 40 mg, LEV 500 = levofloxacin 500 mg + amoxicillin 1 g + pantoprazole 40 mg, LEV 1000 = levofloxacin 1,000 mg + amoxicillin 250 mg + pantoprazole 40 mg, L.M.P = levofloxacin 500 mg + metronidazole 500 mg + pantoprazole 40 mg.

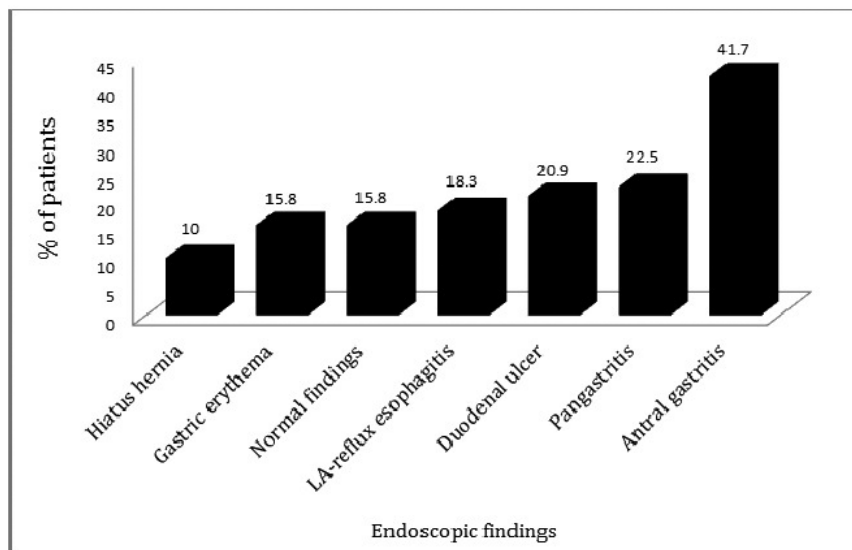


Figure 3. Endoscopic findings of study patients. LA-reflux esophagitis = Los Angeles reflux esophagitis.

a nitroimidazole for 10–14 days or levofloxacin triple therapy consisting of a PPI, levofloxacin, and amoxicillin for 10–14 days are the recommended treatment options by ACG. HP pantocid kit® for a duration of 7–10 days was received by 25% (30/120) of our study patients out of which 33.3% (10/30) had *H. pylori* induced symptoms after treatment completion and only 10% (3/30) were non-adherent to the prescribed regimen. The reason for non-improvement of *H. pylori* induced symptoms may be due to inappropriate duration of therapy, which should have been 14 days instead of 7–10 days or due to inappropriate dose of amoxicillin in

HP pantocid kit® or the patients had prior exposure to macrolides for any reason or eradication rate with clarithromycin-based triple therapy was <85%. In our study, inappropriate dose, duration, and prior exposure to macrolides may be the reason for the non-eradication of *H. pylori* induced symptoms.

Among 17 patients who received the second-line regimens containing levofloxacin, 52.9% (9/17) got relief from *H. pylori* induced symptoms after treatment completion though 88.23% (15/17) were adherent to the prescribed regimen (Fig. 4). One reason for this may be previous exposure to fluoroquinolones

(Pidcock, 1998). According to ACG guidelines, patients should be enquired about previous antibiotic exposure and this information should be incorporated into the decision-making process, but our study patients were not asked about previous antibiotic exposure and either HP pantocid kit® or levofloxacin containing regimens were prescribed empirically without culture and sensitivity or polymerase chain reaction tests to determine resistance pattern of the organism.

In our study, 14.2% (17/120) of the patients were non-adherent to the prescribed *H. pylori* regimens. Medication

non-adherence is one of the obvious factors leading to failure of therapy. Other factors such as cost, side effects of drugs, and polypharmacy may also lead to non-adherence. Patients prescribed *H. pylori* regimens containing a combination of two antibiotics and a PPI have to take three medications at a time which may reduce adherence.

In this study, 14 patients were CLO test negative on repeat endoscopy after 8 weeks of therapy but eight of those patients had *H. pylori* induced symptoms after treatment completion (Table 2). This shows the drawback of the CLO test for *H. pylori* identification. Baseline CLO test was positive only for 80 patients. The remaining patients were included on the basis of histologically proven *H. pylori* infection and GI symptoms. Hence, histology is a better choice than the CLO test for the detection of *H. pylori*. The results of this study point out that histology should be carried out even on patients who are CLO test negative.

The effectiveness of *H. pylori* eradication regimens prescribed in the study patients was 40%. The majority of the patients prescribed *H. pylori* eradication regimens belonged to the age group of 51–60 years with a mean age of 49.2 ± 12.94 years.

Table 1. *H. pylori* induced symptom eradication after treatment completion (n = 120).

Symptoms	No. (%) of patients
Symptom free	71 (59.16)
Symptomatic	49 (40.83)
Dyspepsia	33 (67.34)
GERD*	14 (28.57)
GI blood loss**	2 (4)

*GERD = gastroesophageal reflux disease, **GI blood loss = gastro intestinal blood loss.

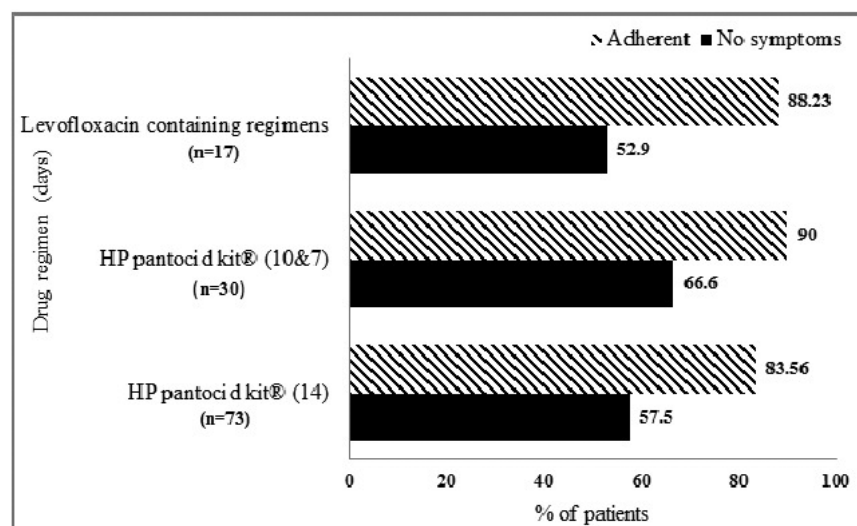


Figure 4. Symptom relief and medication adherence of patients receiving various eradication regimens HP pantocid kit® = clarithromycin 500 mg + amoxicillin 750 mg + pantoprazole 40 mg. Levofloxacin containing regimens: LAP = levofloxacin 250 mg + amoxicillin 1 g + pantoprazole 40 mg, LEV 250 = levofloxacin 250 mg + amoxicillin 500 + pantoprazole 40 mg, LEV 500 = levofloxacin 500 mg + amoxicillin 1 g + pantoprazole 40 mg, LEV 1000 = levofloxacin 1,000 mg + amoxicillin 250 mg + pantoprazole 40 mg, LMP = levofloxacin 500 mg + metronidazole 500 mg + pantoprazole 40 mg.

Table 2. *H. pylori* eradication regimens received by the patients and outcome of therapy (n = 15).

<i>H. Pylori</i> regimen	No. (%) of patients (n = 15)	Repeat CLO test		GI symptoms		Medication adherence	
		No. (%) of patients (n = 15)	No. (%) of patients (n = 15)	No. (%) of patients (n = 15)	No. (%) of patients (n = 15)	No. (%) of patients (n = 15)	No. (%) of patients (n = 15)
		Positive	Negative	Present	Absent	Adherent	Non-adherent
Hp pantocid kit®	11 (73.3)	1 (9)	10 (91)	5 (45.5)	6 (54.5)	10 (91)	1 (9)
Second line regimens	4 (26.7)	0	4 (100)	4 (100)	0	3 (75)	1 (25)

HP pantocid kit® = clarithromycin 500 mg + amoxicillin 750 mg + pantoprazole 40 mg.
Second line regimens

LAP = levofloxacin 250 mg + amoxicillin 1 g + pantoprazole 40 mg,

LEV 250 = levofloxacin 250 mg + amoxicillin 500 + pantoprazole 40 mg,

LEV 500 = levofloxacin 500 mg + amoxicillin 1 g + pantoprazole 40 mg,

LEV 1000 = levofloxacin 1,000 mg + amoxicillin 250 mg + pantoprazole 40 mg,

LMP = levofloxacin 500 mg + metronidazole 500 mg + pantoprazole 40 mg.

Table 3. HP pantocid kit® versus levofloxacin containing regimen in *H. pylori* induced symptom eradication (*n* = 120).

<i>H. pylori</i> eradication Regimens	No. (%) of patients	Symptom eradication No. (%) of patients		<i>p</i> value (chi-square)
		Yes (%)	No (%)	
HP pantocid kit®	103 (85.8)	62 (60.2)	41 (39.8)	0.573
Levofloxacin containing regimens*	17 (14.2)	9 (52.9)	8 (47.1)	

HP pantocid kit® = clarithromycin 500 mg + amoxicillin 750 mg + pantoprazole 40 mg.

*Levofloxacin containing regimens

LAP = levofloxacin 250 mg + amoxicillin 1 g + pantoprazole 40 mg.

LEV 250 = levofloxacin 250 mg + amoxicillin 500 + pantoprazole 40 mg.

LEV 500 = levofloxacin 500 mg + amoxicillin 1 g + pantoprazole 40 mg.

LEV 1000 = levofloxacin 1,000 mg + amoxicillin 250 mg + pantoprazole 40 mg.

LMP = levofloxacin 500 mg + metronidazole 500 mg + pantoprazole 40 mg.

Occurrence of *H. pylori* infection in developing nations is 80% in adults over 50 years of age and infected persons normally obtain *H. pylori* before 10 years of age and grow up with the infection (Chey *et al.*, 2017). In the study patients, the male gender was predominant which may be due to the fact that the majority of the patients undergone endoscopy were males. Though more number of patients using clarithromycin containing regimen got relief of symptoms as compared to levofloxacin containing regimen, the difference was not significant (Table 3). CLO or histology tests could not be performed on all the patients after completion of therapy and culture and sensitivity analysis to determine the resistance pattern of *H. pylori* was not performed and these are limitations of our study.

CONCLUSION

Most of the patients with dyspeptic symptoms were found to have *H. pylori* infection confirmed by CLO test or histology. Majority of the patients were treated with *H. pylori* eradication regimen containing clarithromycin, amoxicillin, and pantoprazole and got symptom relief. This regimen was found to be more effective than levofloxacin containing regimens in *H. pylori* symptom eradication. However, overall therapy was unsatisfactory due to inappropriate dose, duration, or sub-optimal adherence. Bismuth containing regimens were not prescribed to any of the patients.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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