The efficacy of dual therapy for eradicating *H. pylori* in a Colombian population

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Abstract

Background: *Helicobacter pylori (H. pylori)* affects 50% of the human population. The efficacy of the usual treatments has decreased due to increased antibiotic resistance, except for that of amoxicillin, tetracycline, furazolidone and bismuth. Recently, there has been a new interest in dual therapy with high-dose proton pump inhibitors (PPI) and amoxicillin as initial and rescue treatment. There are no studies on this topic in our setting.

Objective: to determine the efficacy of dual therapy with high-dose IPP and amoxicillin for eradicating *H. pylori*.

Materials and methods: this was a quasi-experimental study carried out from December 2019 to July 2020 in people over the age of 18 with histologically confirmed *H. pylori*. All received 40 mg of esomeprazole half an hour before breakfast, lunch and dinner, plus 1 gram of oral amoxicillin every eight hours for 14 days. Eradication was determined by fecal antigens (OnSite™ *H. pylori* Biotech Inc.) after four weeks of treatment.

Results: 108 patients with an average age of 67 years were included, 70% of whom were women. Eradication per protocol (PP) and intention to treat (ITT) was 86% (95%CI 79.4-92.5%) for both. In previously treated patients (26%) the efficacy was 85.7% (95%CI 71.8-99.5%). Adverse events were mild in 31%, especially nausea (16%) and abdominal distension (14%). Treatment was not suspended in any patient.

Conclusion: Dual therapy is effective, easy to administer, and has few adverse effects. It would be a good option in our setting as initial or rescue therapy. Larger studies are needed to confirm our results. **(Acta Med Colomb 2021; 46. DOI: https://doi.org/10.36104/amc.2021.2091).**

Keywords: *Helicobacter pylori, dual therapy, proton pump inhibitor, amoxicillin*.

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Introduction

More than 50% of the world's population is infected with *Helicobacter pylori (H. pylori),* with Latin America having the second highest prevalence after Africa (1, 2).

Chronic gastritis develops in all those who are infected, which may lead to peptic ulcers, atrophic gastritis, gastric adenocarcinoma and gastric MALT lymphoma. Less frequently, *H. pylori* may also cause vitamin B12 deficiency anemia and immune thrombocytopenia (3-4). *H. pylori* eradication cures gastritis and may alter the long-term progression of these complications; therefore, all infected persons should be treated (5).

An anti *H. pylori* treatment is considered recommendable when it has 90% intention-to-treat (ITT) efficacy and 95% efficacy by protocol (BP) (6). Treatment failure is mainly due to the high rate of resistance to the most commonly used antibiotics (3). Other factors which result in treatment failure are noncompliance, insufficient inhibition of acid secretion, and the fact that *H. pylori* has several growth niches which require extended treatment with antibiotics able to reach these sites (7, 8). In Latin America, high rates of resistance to clarithromycin, metronidazole and levofloxacin have been documented. Therefore, the current recommendation is to use quadruple therapy (a proton pump inhibitor plus three antibiotics) with or without bismuth, for 14 days (7, 9-11). In Colombia, studies have determined that the rate of resistance to clarithromycin is greater than 20%, to levofloxacin is 27.3% and to metronidazole is greater than 80%; thus, the recommendation in our country is to add bismuth subsalicylate two or three times a day to 14-day triple therapies which include these antibiotics (7, 12-14).

Profound acid inhibition favors improved activity of acid-sensitive antibiotics like amoxicillin and greater replication of *H. pylori,* making it more vulnerable to antibiotics (15-17).

H. pylori is rarely resistant to amoxicillin (less than 5%);

however, this antibiotic is very unstable in an acid pH and, therefore, its efficacy can be maintained as long as profound acid inhibition is achieved (reaching a gastric pH greater than or equal to six) and therapeutic serum levels are maintained for 24 hours, which requires administration three or four times a day (18, 19). In 1995, Bayerdörfer et al. showed that treatment with high doses of amoxicillin (750 mg three times a day) and omeprazole (40 mg three times a day) had a greater than 90% efficacy in patients with peptic ulcer or gastric MALT lymphoma (20, 21). However, this regimen became less important with the advent of triple therapies with amoxicillin (twice a day) and clarithromycin (twice a day) or metronidazole, but with high rates of resistance to antimicrobials, interest in dual therapy with amoxicillin and a PPI has revived (22).

Recent findings indicate that this treatment has an efficacy of at least 90%, regardless of whether bismuth salts are added (18, 23-25). Lou Yu et al. compared the eradication rate of dual therapy (esomeprazole 40 mg twice a day plus amoxicillin 1 gm three times a day) with or without bismuth, with intention to treat eradication rates of 88.8 - 92.5% at a Chinese medical center. Yang J et al. also found similar eradication rates between dual therapy (esomeprazole 20 mg four times a day plus amoxicillin 750 mg four times a day) and quadruple therapy with bismuth which were 91.1-91.2%, respectively, in the intention to treat (ITT) analysis (15, 24, 26).

The capacity of PPIs to block acid production depends on their metabolism by the hepatic CYP2C19 enzyme (27-29). There are four different phenotypes, based on the rate of PPI inactivation or metabolism: ultrarapid, rapid or extensive, intermediate and slow metabolizers (27, 30). A recent clinical trial in Colombia determined that 62.4% of the subjects were rapid metabolizers and 21.1% were ultrarapid (30). This finding means that to eradicate *H. pylori* in our setting, higher doses of CYP-dependent PPIs (lansoprazole, omeprazole and pantoprazole) will be required, or non-CYP dependent PPIs (esomeprazole or rabeprazole) (27-29) or third generation PPIs which block potassium in the gastric ATPase, such as vonoprazan, which is only available in Japan (16, 31).

In 2015, a study in Taiwan evaluated the combination of rabeprazole (20 mg twice a day) plus amoxicillin (750 mg four times a day), finding 95.3% cure rates in patients with no prior treatment and 89.3% in patients with prior treatment (25). In contrast, in China, another study using this last regimen with rabeprazole did not achieve the minimum efficacy rate required (19).

Much more recently, the first randomized clinical trial comparing dual therapy with vonoprazan 20 mg twice a day and amoxicillin 750 mg twice a day for seven days with or without clarithromycin found intention to treat eradication rates of 87.1 and 90.2%, a difference which was not statistically significant (31).

This study aimed to evaluate the efficacy of dual therapy with high doses of esomeprazole and amoxicillin as first-line or rescue treatment for eradicating *H. pylori* in the Colombian population, as well as describe the adverse effects of this therapeutic regimen.

Materials and methods

Study design and population

A quasi-experimental prospective study was performed at the Centro de Gastroenterología y Endoscopia Digestiva in Bogotá, Colombia, affiliated with the graduate gastroenterology program at Universidad Nacional de Colombia from December 2019 to July 2020.

Inclusion criteria

Patients were included who were over the age of 18; referred to upper GI endoscopy (EGD) with a diagnosis of dyspepsia, gastroesophageal reflux disease or anemia; and who had histological identification of *H. pylori*, regardless of whether they had received prior eradication treatment. All the patients signed informed consent.

Exclusion criteria

Patients with a history of gastric MALT lymphoma or gastric cancer, who were allergic to penicillin or proton pump inhibitors, or who had undergone upper gastrointestinal surgical resections.

Intervention

All patients underwent a routine EGD, with a minimum of eight hours of fasting. All had the procedure done under sedation (propofol and remifentanil) administered by an anesthesiologist. Biopsies of the body and antrum were taken during the procedure, following the Sydney protocol (32). Briefly, two biopsies were taken from the body, two biopsies from the antrum and one biopsy from the incisura, which were sent in separate, appropriately marked jars, in which, besides determining the presence of *H. pylori,* the severity of the chronic gastritis was stratified using the Operative Link on Gastritis Assessment (OLGA) system (33). Once the biopsies were taken, they were fixed in 10% formalin and sent to pathology. The pathology assessment followed the standard process of embedding them in paraffin, and multiple five-micron sections were obtained from each sample, which were stained with hematoxylin and eosin (HE). If *H. pylori* was not found, the samples were studied further with Giemsa staining (34). The demographic variables, comorbidities, endoscopic findings and treatment efficacy were recorded in a data collection tool designed for this study.

Treatment

All patients received 40 mg of esomeprazole half an hour before each meal and 1 gram of amoxicillin every eight hours (7 a.m., 3 p.m. and 11 p.m.) for 14 days. The patients were evaluated four times throughout the study. At the beginning of treatment during an on-site appointment. During the first assessment, general information, the reason for the endoscopy, and medical history were recorded, and dual therapy was pre-

scribed, explaining clearly and understandably the importance of the treatment and the correct way to follow the prescription. The second assessment was an on-site appointment 15 days after finishing treatment. During this appointment, the occurrence of adverse effects was ascertained and whether treatment had been suspended, as well as whether any doses of treatment had been omitted. During this appointment, the patients were given an order for fecal antigens to be taken four weeks or more after finishing treatment, to determine its efficacy. During the study, the patients were instructed to call two of the investigators (EJB and CR) immediately if they experienced any adverse effect and if they decided to suspend treatment. The adverse effects were evaluated using a questionnaire applied at the end of treatment and were classified as mild (transient and well tolerated), moderate (discomfort which partially interfered with daily activities) and severe (significantly interfered with daily activities).

During the last assessment six weeks after treatment, the results of the fecal antigen test were reviewed to determine cure or treatment failure.

Verification of eradication

H. pylori eradication was determined using fecal antigens four weeks after finishing treatment. Fecal antigens were measured using the Biotech Inc. OnSite™ *H. pylori* test, which is a lateral flow chromatographic immunoassay which qualitatively detects the *H. pylori* antigen using specific antibodies. The samples approved as matrices for the test are solid, semisolid and liquid feces which are transported in hermetically sealed containers and stored at 2-8°C until the test is run. The sample should be tested as soon as possible, but may be held up to 72 hours. The test was processed in a microbiology laboratory in which the procedure has been standardized. The results are interpreted as negative if only the C line appears, positive if the T line also appears, and invalid if the blue line does not appear, in which case the test should be repeated with the same sample to eliminate potential error (35). For the fecal antigen test, patients should have stopped the PPIs at least 15 days prior to running the test, and antibiotics at least one month prior, to avoid false negatives (7).

Sample size calculation

The sample size was calculated with Epidat version 4.1, using the module/sampling/sample size calculation/hypothesis contrast/comparison of proportions path for paired groups. The parameters included were: expected proportion in population 1 (73% eradication of *H. pylori* with standard treatment) (15, 16), expected proportion in population 2, 90% efficacy (efficacy of dual therapy) (12), 95% confidence level and 80% power, for which a minimum of 84 pairs is required. The different study variables are shown in Table 1.

Statistical analysis

The data base was recorded in Excel version 2013. Univariate analysis was performed through statistical description, determining absolute and relative frequencies for the qualitative variables; and measures of central tendency, measures of dispersion or measures of position (using the mean and standard deviation when numeric variables followed a normal distribution, or median, interquartile range and percentiles when they did not) for quantitative variables. Cure rates are expressed as proportions (percentages) with their respective confidence intervals. Descriptive analyses of the frequency of positive and negative fecal antigens were performed according to adverse effects and tobacco and alcohol consumption. Additionally, a difference in proportions test was carried out to evaluate the differences in the success of dual therapy in the group of patients who used tobacco, those who used alcohol, and those with adverse effects. The Chi^2 test in Stata 14 was used to evaluate this difference in proportions. Significance was set at 0.05 or less.

Objectives

The objective of this study was to determine the eradication rate of *H. pylori* with dual therapy (high dose PPI and amoxicillin) and evaluate its adverse effects.

Ethical considerations

The research protocol and informed consent were approved by the Ethics and Research Committee of the Universidad Nacional de Colombia School of Medicine.

Results

A total of 108 patients met the inclusion criteria, with an average age of 67 years; 70% were women. There were no losses to follow up (Figure 1). Forty-nine percent were overweight (defined by body mass index) and 16% had class I obesity. Endoscopic findings were as follows: chronic gastritis 100%, erosive esophagitis 33%, erosive duodenitis 14%, and gastric ulcer 4%. The OLGA results were: OLGA 0/IV 88%, OLGA I/IV 10%, and OLGA II/IV 2%. No patients had OLGA IV (Table 2).

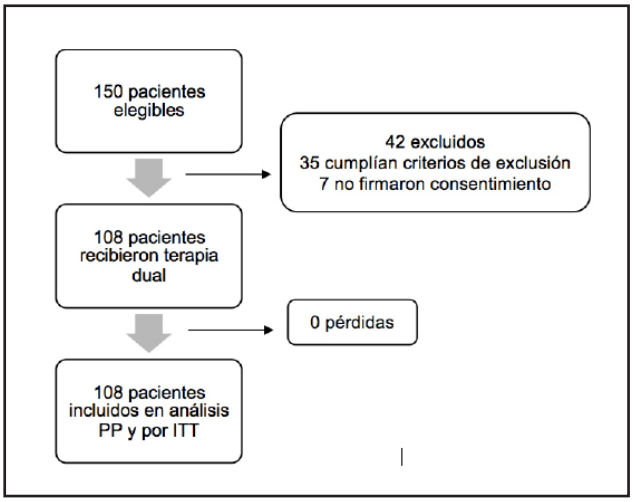

Figure 1. *Flow chart of the patient selection process.*

The *H. pylori* eradication rate was 86% (93/108; 95%CI 79.4-92.5%) for both ITT and BP (Table 2). Fourteen percent of the patients experienced treatment failure, of whom 60% were overweight and 14% were obese. Fifty-six percent of the patients had not received prior treatment and 26% (28/108) had received some treatment regimen. In patients with prior treatment, *H. pylori* was eradicated in 85.7% (24/28; 95%CI 71.8 - 99.5%) (Table 3). Adverse events occurred in 31% of the patients, with the most frequent being nausea (16%) and abdominal distention (14%). There were no serious adverse events or events which forced treatment suspension (Tables 2 and 4).

A comparison of the eradication rate between the group with adverse events and those without showed a statistically significant difference (p= 0.05), with a higher eradication rate in those without adverse events. A difference was also found with the alcohol and tobacco consumption group, with a lower eradication rate in those who were exposed.

Discussion

In this study, which, as far as we found, is the first to describe dual therapy for *H. pylori* eradication in Latin America, we found an overall eradication rate of 86% (95%CI 79.4-92.5%) for both ITT and BP, with no differences in patients who had had prior treatment failure (85.7% 95%CI 71.8-99.5%). The overall results are similar to those found by Hu (19).

Esomeprazole was selected for use in this study in light of the high prevalence of rapid and ultrarapid first-generation PPI (omeprazole, pantoprazole, lansoprazole) metabolizers in our setting, which, combined, exceed 80% and are a known cause of treatment failure (30, 36). With this medication, we would theoretically avoid one cause of therapeutic failure. Amoxicillin was administered three times a day and, like other investigators, we do not know if administering it four times a day (1 gr or 750 mg) could increase its efficacy (37). However, neither gastric pH nor plasma amoxicillin levels were confirmed; thus, it is possible that increasing the frequency of amoxicillin and/or PPI (up to four times a day) could achieve a higher success rate, as reported in Tang and Tai's studies (25, 38). Optimization of eradication therapies by increasing gastric pH to more than six and increasing the frequency of amoxicillin has been shown to improve success, considering that its bactericidal effect is dose dependent (15-17).

A recent meta-analysis (37) published during the conduction of this study found that the success of this dual therapy has a similar efficacy to the quadruple therapies recommended by the main *H. pylori* management guidelines (3, 6). In that important meta-analysis (33), most of the studies

Table 1. *Study variables and variable definitions.*

Variable	Type	Scale	Category
Age	Quantitative	Ratio Discrete	Years of age
Sex	Qualitative	Nominal Dichotomous	Male Female
Place of residence	Qualitative	Nominal Dichotomous	Rural Urban
History	Qualitative	Nominal Dichotomous	Medical history
Reason for endoscopy	Qualitative	Nominal Dichotomous	Specific reason (e.g., dyspepsia)
H. pylori infection	Qualitative	Nominal Dichotomous	Present Absent
OLGA histological classification	Qualitative	Nominal Polychotomous	I II III IV
Previous treatment for *H. pylori*	Qualitative	Nominal Dichotomous	Yes No
Finished treatment with dual therapy	Qualitative	Nominal Dichotomous	Finished Did not finish
Reason for discontinuing treatment	Qualitative	Nominal Polychotomous	Specific reason for discontinuing treatment
Side effects	Qualitative	Nominal Polychotomous	Specific side effect (abdominal pain, vomiting, rash)
Fecal antigens four weeks after dual treatment	Qualitative	Nominal Dichotomous	Positive Negative
Cure	Qualitative	Nominal Dichotomous	Yes No
Treatment failure	Qualitative	Nominal Dichotomous	Yes No

Table 2. *Demographic and clinical characteristics of the population.*

Variable	Population (n=108)
Age n (Range)	67 (30-85)
Sex	
Female n (%)	76 (70)
Male n (%)	32 (30)
BMI n (%)	
Normal	38 (35.2)
Overweight	53 (49.1)
Class 1 obesity	17 (15.7)
Alcohol n (%)	3 (2.78)
Smoking n (%)	4 (3.7)
Fecal antigens	
Negative n (%)	93 (86)
Positive n (%)	15 (14)
Prior treatment n(%)	
Yes	28 (26)
No	61 (56)
Does not recall	19 (18)
OLGA classification n (%)	
OLGA 0	95 (87.9)
OLGA 1	10 (10.8)
OLGA >1	3 (2.8)

Table 3. *Eradication rate.*

	Total (n=108)	Prior treatment
ITT and BP	86% (93/108)	85.7% (24/28)
95% CI	79.4% – 92.5%	71.8% - 99.5%
ITT, intention to treat; BP, by protocol.		

Table 4. *Adverse events.*

Adverse events n (%)	34 (31.5)
Nausea	17 (15.7)
Bloating	15 (13.4)
Abdominal pain	9 (8.3)
Headache	9 (8.3)
Diarrhea	8 (7.4)
Vomiting	4 (3.7)
Rash	3 (2.8)

included were Asian, making it difficult to extrapolate to the Western population, including Latin America. The current study contributes towards filling the information gap on the use of this treatment in our setting, and its results support the current recommendation of using it not only as first line treatment, but also as rescue therapy, since both cases had similar eradication (37, 39).

Other factors which have been associated with a lower response to recognized treatments for eradicating *H. pylori* are smoking and alcohol consumption (40). Smoking is associated with a lower eradication rate as it reduces gastric arterial flow and increases the secretion of hydrochloric acid, keeping amoxicillin from working properly (41, 42). In our population, the rate of smoking and active alcoholism was low, although it might be underestimated due to memory bias. Although the study was not designed to find associations, differences were found in the group that used alcohol and tobacco ($p<0.05$), with a lower eradication rate in those who were exposed. Yan (18) showed that adding bismuth to dual therapy only improved the response rate of smokers. The adverse events of the medications used for eradicating H. pylori increase the desertion rate and concomitantly affect the success rate (6, 7). The different studies evaluating the effectiveness of dual therapy have consistently shown that it is the treatment with the fewest adverse effects (37, 39), which is also seen in our study in which 31% of the patients experienced adverse effects, but none of them were serious or led to discontinuing treatment. The severity of chronic gastritis found in this study, according to the OLGA score, is similar to that of a Colombian study with more than 1,500 patients, in which most of the patients (88%) had 0-II severity, meaning low risk of stomach cancer in the future; therefore, once H. pylori is eradicated, there would be no need for endoscopic monitoring, as opposed to grades III and IV (42). Thus, we believe it is very important to determine the severity of the atrophy or intestinal metaplasia, in addition to seeing if H. pylori is present, in all endoscopies, as this identifies patients who require follow up endoscopies due to a risk of stomach cancer (3, 5).

Considering that *H. pylori* amoxicillin resistance is very rare worldwide and in Colombia, this would be an excellent option due to its easy administration and, even more, because in our setting, as well as in Latin America and other parts of the world, cultures are not available for selecting first line therapy for eradicating *H. pylori* (as has been recommended by experts) (3, 6, 7). In addition, its easy administration would allow for better treatment compliance and, likewise, the microorganism's resistance to antibiotics would not be increased. We believe further studies with a greater number of patients would be needed to verify this efficacy and probably determine the frequency of administration and dose of amoxicillin and/or PPI which would achieve the greatest success rates.

In conclusion, our findings show that dual therapy with high dose amoxicillin and PPI is an effective and safe treat-

ment both for first-time treatment ("naive" patients) and for patients with one or two prior failed treatments.

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