Randomized study comparing standard first line 10 day therapy against *Helicobacter pylori* including clarithromycin versus standard first line therapy with levofloxacin

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Abstract

Background: Evidence is mounting that the standard triple therapy against H. pylori infections has been losing clinical effectiveness, but triple therapy with levofloxacin, amoxicillin, and a proton pump inhibitor is effective and well tolerated. This scheme has been suggested as an alternative for standard first-line therapy. The purpose of this randomized, multicenter, controlled study is to compare rates of successful eradication of standard triple therapy using clarithromycin, amoxicillin and omeprazole (CAO) and triple therapy using levofloxacin, amoxicillin and omeprazole (LAO). Materials and Methods: A total of 317 patients who had been diagnosed with H. pylori infections through biopsies were randomized into two groups. One group of 160 patients was assigned a 10 day CAO treatment regimen and the other group of 157 patients was assigned a 10 day LAO treatment regimen. Eradication was assessed by optimized breath test. Adverse effects and toleration were also assessed. Results: Intention to treat analysis gave the following results: CAO, 68.8% (110/160) and LAO, 84.1% (132/157) with p = 0.0021. The CAO eradication rates was 71.9% (105/146) and the LAO eradication rate was 89.3% (125/140) with p = 0.0004. There were significant statistical differences in effectiveness between the two treatment groups, but there were no significant differences in toleration and adverse effects between the two groups. Conclusions: Treatment of H. pylori infections with triple therapy based on levofloxacin was a better alternative than clarithromycin-based triple therapy in this study.

Key words

Helicobacter pylori, therapy, claritromycin, levofloxacin.

INTRODUCTION

Helicobacter pylori (H. pylori) infection is the major cause of chronic gastritis, peptic ulcers, gastric adenocarcinoma, and mucosa-associated lymphoid tissue (MALT). It is therefore imperative to move towards effective bacterial eradication (1, 2).

Current guidelines for the eradication of *H. pylori* in Europe and North America recommend therapeutic regimens that achieve over 80% eradication rate by intention-to-treat analysis, preferably by using a proton pump inhibitor plus two antibiotics (clarithromycin plus amoxicillin) (3, 4).

Clarithromycin was once recognized as the most powerful antibiotic with bacteriostatic effects against *H. pylori* (5). Unfortunately, primary resistance to clarithromycin is increasing worldwide, and is considered to be the primary factor reducing efficacy against *H. pylori* (6, 7). Even with the most effective therapeutic regimens that include a proton pump inhibitor (PPI), and two antibiotics, up to 20-30% of treatments fail and *H. pylori* infections persist (8). *H. pylori* eradication prevents recurrence of duodenal ulcers, and reduces the risk of gastric cancer (9). Recently, we have shown that in our region 7 to 10 day treatment with clarithromycin did not achieve optimal levels of bacterial eradication. After almost 30 years implementing vari-

ous treatments of *H. pylori*, the ideal treatment regimen has yet to be defined (7).

Currently, clarithromycin-based therapies seem to offer insufficient eradication rate in some regions, thus other alternatives have been evaluated. Levofloxacin presents outstanding in vitro activity against *H. pylori* and has emerged as a promising alternative. However, levofloxacin has been evaluated more as a second line therapy when one or more therapies against *H. pylori* have failed. Eradication rates achieved with this treatment have been between 75% and 86%. Other studies have evaluated small numbers of patients treated with a combination a PPI, amoxicillin, and levofloxacin as a first-line therapy (10-12). Some but not all of these studies have shown excellent results with eradication rates between 85% and 92% (12-17). Although levofloxacin offers an excellent safety profile, resistance of *H. pylori* to this quinolone has been reported recently, and this could jeopardize its use in the future (18-20).

The primary objective of this study is to evaluate and compare the clinical effectiveness of standard triple therapy using clarithromycin, amoxicillin, and omeprazole with an alternative regimen that replaces clarithromycin with levofloxacin as a first-line therapy. Secondary objectives are evaluation of the effectiveness of eradication by endoscopic diagnosis and histology by estimating the load of *H. pylori,* and to perform controlled clinical trials in patients with ulcer and non-ulcer dyspepsia one year after treatment.

METHODS

This study is a randomized open clinical trial conducted on outpatients of an urban population between January 2008 and July 2011. Study characteristics were presented in a recent publication (7).

Study population

Patients were over 18 years old and 70 years old or younger who had *H. pylori* infections histologically confirmed by endoscopy and detected by hematoxylin and eosin staining of samples. We excluded patients with clinical records of gastrectomy, peptic ulcer complications such as stenosis or bleeding, pregnant or nursing women, patients with endoscopic findings of MALT lymphoma or gastric cancer, and patients who had received any prior treatment for *H. pylori.*

To prevent interference with the treatment against *H. pylori*, we excluded patients with a history of use within the previous month of antibiotics, bismuth compounds, H2-receptor antagonists, probiotics or PPIs. In addition, we excluded patients with major psychiatric disorders, allergies to penicillin and concurrent histories of malignant disease, liver or kidney failure.

Clinical study design

The study was conducted on patients from various hospitals and private practices in the city of Medellin whose biopsies were positive for *H. pylori*. We assessed two standard 10 day therapies to eradicate *H. pylori*: clarithromycin, amoxicillin and omeprazole (CAO), and levofloxacin (Truxa ®), amoxicillin, and omeprazole (LAO). For sample selection we assumed a difference of population proportions was used. We assumed a 0.05 type I error, a 0.2 type II error, a 0.9 ratio of eradication effectiveness for the group treated with levofloxacin, a 0.78 ratio of eradication effectiveness for the group treated with clarithromycin, 0.12 as an absolute difference between proportions, and 1 as the allocation rate between groups. Using these parameters "Sample Size" version 1.1 calculated a sample size of 140 patients per study group.

Demographic characteristics of the patients were evaluated. Endoscopy findings of non-erosive gastritis, erosive gastritis, gastric ulcers, and duodenal ulcers were considered. Infection densities of *H. pylori* based on histological examination with at least 2 antral biopsies were categorized into two groups: low (1 or 2 cross matches) and heavy (3 or 4 cross matchs). Only hematoxylin and eosin staining of samples was used.

We performed a follow-up examination one to three weeks after treatment completion. It evaluated whether patients had adverse effects related to the treatment or tolerated treatment, and it evaluated whether treatment was completed. Completion was defined as patient having finished more than 70% of the prescription.

Study groups

Patients received triple therapy. They were randomly assigned into two groups. Group 1-CAO consisted of those patients who received 500 mg clarithromycin, 1 g amoxicillin, and 20 mg omeprazole for 30 days. Group 2-LAO consisted of those patients who received 500 mg Truxa ® levofloxacin, 1 g amoxicillin, and 20 mg omeprazole for 30 days. All medications in both groups were administered orally. At the time the study began the only levofloxacin available in the market was Truxa® which was used throughout the study. A randomization sequence was generated by EPIDAT® 3.1 statistical package. On the basis of that sequence treatment was assigned to each patient. Patients were asked not to smoke during treatment.

Eradication evaluation

Patients underwent an optimized breath test at the Clinical Hematology Laboratory in Medellin, Colombia from 4 to

6 weeks after completion of treatment. Optimized carbon-labeled urea (^{13}C-urea) breath tests have 100% sensitivity, specificity, positive predictive value and negative predictive value (21).

As the primary outcome measure, eradication of *H. pylori* infection was defined as a negative result for a ^{13}C-labelled urea breath test. As a secondary outcome measure, we evaluated completion of treatment defined as 70% or greater completion of prescribed treatment. This measure was evaluated at follow up appointments after the end of antibiotic therapy. Protocol and intention-to-treat analyses were also taken into account as secondary outcome measures.

Breath tests were conducted by a blinded researcher who did not know which treatment patients were receiving.

Evaluation after one year of treatment

Clinical conditions of patients were assessed at the time of prescription and one year after *H. pylori* eradication treatment. The assessment was based on the Rome III criteria for functional gastrointestinal disorders in adults. Clinical conditions were recorded after a year of therapy and determined to be better, the same or worse. In addition, the one year evaluation placed special emphasis on the initial endoscopic diagnosis of the patient, and the relationship of eradication of *H. pylori* with the patient's clinical condition at the end of the assessment year.

Statistical analysis

For the descriptive analysis, absolute and relative distributions as well as summary measures (arithmetic means and standard deviations) were used. The demographic characteristics of both groups were compared using confidence intervals for the differences in proportions of independent samples. The eradication rate of *H. pylori* was analyzed by intention-to- treat (ITT), and per-protocol population (PPP) analyses. All patients in the study were evaluated by ITT. The PPP was only considered for patients with full treatment. The differences in eradication rates of *H. pylori,* and 95% confidence intervals were calculated for IIT and PPP. The eradication of *H. pylori* in the CAO therapy (group 1) was expected to be lower than that in the LAO therapy (group 2). A 12% non-inferiority margin was determined on the basis of previously described controlled trials (17, 20). The incidence of adverse in the two groups was compared using the difference in proportions for independent samples under the assumption of normal statistical distributions of these differences. After one year of treatment, clinical responses were assessed by comparisons of chi-square values (P) of the two treatment groups. Values of $P < 0.05$ were considered to be statistically significant.

Ethical issues

This research was classified according to the International Declaration of Helsinki, the Belmont Report, and Colombian Resolution 8430 of 1993 as an investigation without biological, physiological, psychological or social risks. Resolutions from 1995 to 1999 which establish standards for handling of medical records were also taken into account.

RESULTS

Patients

Between January 2008 and July 2011 a total of 317 patients were treated for eradication of *H. pylori*. The patients were diagnosed with *H. pylori* by endoscopic biopsies taken in the month prior to commencement of therapy. 160 out of the 317 patients were randomized to CAO treatment group (group 1), and 157 patients were randomized to LAO therapy (group 2). Endoscopic findings of gastritis, erosive gastritis, gastric ulcers and duodenal ulcers were similar for the two treatment groups. No significant demographic differences were found between the two groups (Table 1).

Table 1. Sociodemographic and clinical characteristics of treatment groups.

	CAO (n=160)	LAO (n=157)	p
Age (years)	48,7± 11,5	47,8 ± 14,2	0,346
Gender (male / female)	54 /106	46 / 111	0,232
Diagnosis (NUD / peptic ulcer)	106 / 54	93 / 64	0,535
Gastritis (%)	106 (66,2)	93 (59,2)	
Erosive gastritis (%)	32 (20)	37 (23,6)	
Duodenal ulcers (%)	10 (6,2)	15 (9,6)	
Gastric ulcers (%)	12 (7,6)	12 (7.6)	
H. pylori (scarce / abundant)	77 / 83	79 / 78	0,390
Breath test (not eradicated / eradicated) by intention-to-treat	50 / 110	25 / 132	*0,001*
Breath test (not eradicated / eradicated) by protocol	41 / 105	15 / 125	*0,000*
Adverse effects (YES / NO)	45 / 115	51 / 106	0,704
Intolerance (YES / NO)	14/146	17/140	0,332
Intestinal metaplasia (YES / NO)	24 / 136	26 / 131	0,410
Atrophy (YES / NO)	19 / 141	15 / 142	0,314

Eradication rates

The eradication rate of patients treated with CAO was lower than that for patients treated with LAO in both IIT and PPP analyses: Nevertheless, only LAO therapy achieved optimal figures for bacterial eradication (Table 2).

Table 2. Eradication rates for both groups.

	CAO (n=160)	LAO (n=157)	p
Intention-to-treat analysis			
Successful eradication	110/160	132/157	*0,001*
Eradication percentage	68,8%	84,1%	
Protocol analysis			
Successful eradication	105/146	125/140	
Eradication percentage	71,9%	89,3%	*0,000*

By determining whether eradication rates were related to the degree of infection by *H. pylori* according to biopsy reports, we found that the eradication rate was similar for both therapies regardless of bacterial load (Table 3).

Table 3. *H. pylori* eradication and relationship to the degree of infection.

	CAO		p	LAO		p
	Eradicated	Not eradicated		Eradicated	Not eradicated	
H. pylori scarce	52	25		64	15	
H. pylori abundant	58	25		68	10	
Total	110	50	0,201	132	25	0,440

No significant differences in degrees of *H. pylori* infections were observed between NUD endoscopic findings and UD endoscopic findings (Table 4).

Table 4. Endoscopic findings and degree of *H. pylori* infection.

	NUD	UD	Total	p
H. pylori scarce	98	58	156	
H. pylori abundant	101	60	161	
	199	118	317	0,540

NUD: non-ulcer dyspepsia. UD: ulcer due to dyspepsia.

Adverse reactions

Medical treatment of 14 of the 160 patients treated with the CAO scheme was discontinued because of intolerance. Similarly, medical treatment of 14 of the 157 patients treated with the LAO scheme was discontinued because of intolerance. For PPP analysis, we included 146 patients from the CAO group, and 143 patients from the LAO group. Adverse effects were observed in 33.1% of patients treated with CAO, and 41.4% of those treated with LAO with no significant difference observed (p=0.392).

The most common symptoms for both groups were epigastric pain, nausea and vomiting (with metallic taste in patients' mouths), myalgia, diarrhea and skin rash. There were no significant differences between the two groups (Table 5).

Table 5. Adverse effects in each treatment group.

	CAO (n=160)	LAO (n=157)	p
Nauseas & Vomiting (%)	22 (13,8)	21 (13,4)	
Epigastric pain (%)	20 (12,5)	27 (17,2)	
Myalgia	4 (2,5)	11 (7,0)	
Diarrhea (%)	5 (3,1)	5 (3,2)	
Rash (%)	2 (1,2)	1 (0,6)	
Adverse effect total (%)	53 (33,1)	65 (41,4)	0,329

Response to eradication therapy according to initial diagnosis

There was a similar rate of eradication for both therapy regimens and for different endoscopic findings (Table 6).

Table 6. Response to therapy according to endoscopic findings.

	CAO		LAO		Total	p
	Eradicated	Not eradicated	Eradicated	Not eradicated		
Gastritis	75	31	78	15	209	
Erosive gastritis	19	13	30	7	69	
Gastric ulcer	11	1	12	0	24	
Duodenal ulcer	5	5	12	3	25	
Total	110	50	132	25	317	0,439

One-year follow-up

Patients were contacted in person or by telephone to review their gastrointestinal manifestations a year after receiving therapy. Gastrointestinal manifestations were classified according to the Rome III diagnostic criteria. We recorded whether symptoms had improved, worsened, or were the same one year after treatment. We emphasized whether initial diagnosis was functional dyspepsia or if endoscopy had indicated peptic acid disease with a structural component such as erosions or ulcers. No significant differences were found between clinical manifestations related to the two treatment regimens at the one-year follow-up analyses.

Nevertheless, our assessment of clinical responses in relation to the initial diagnoses found 78.4% of the 100 patients with non-ulcer dyspepsia improved while symptoms of 79.6 % of the 118 patients with ulcers due to dyspepsia (duodenal ulcers, erosive gastritis, or gastric ulcers) improved (Table 7).

Table 7. Evaluation of clinical behavior one year after treatment against *H. pylori* according to initial diagnosis.

	NUD	UD	Total	p
Better	156	94	250	
Same or worse	43	24	67	
Total	199	118	317	0,789

NUD: non-ulcer dyspepsia. UD: ulcer due to dyspepsia.

DISCUSSION

This randomized, controlled, multicenter study included a total of 317 patients. It shows that in a country that has shown a high prevalence of clarithromycin resistance (greater than 15%) the rate of eradication with levofloxacin triple therapy is superior to standard triple therapy with clarithromycin with statistically significant results.

When planning treatment of an *H. pylori* infection, a physician should ideally be aware of the local and regional prevalence of antimicrobial resistance as well as of the efficacy of treatment in the physician's daily practice. Unfortunately, there are no studies of the sensitivity of *H. pylori* in Medellin however a local study has suggested that therapy with clarithromycin for 7 or 10 days is not useful (7). This could be explained by the increasing resistance of *H. pylori* to clarithromycin, as has been suggested by sensitivity studies elsewhere in the country (22).

While meta-analyses support the use of Levofloxacin, (10) it has been most frequently used as a second-line therapy (23-25) or even as a third-line therapy (26) when standard therapies with clarithromycin and metronidazole have failed (16, 27-29). Success has even been described with short 5 day treatment regimens. [30] However, Levofloxacin's role in first-line therapy has not been evaluated in our environment, although there are reports in the literature suggesting that it could be effective here (20, 31, 32), albeit with limitations (33) 3% primary resistance to levofloxacin has been reported elsewhere (34).

Recently, a Taiwanese study compared use of CAO and LAO regimens for first-line and second-line therapy. It showed superior effectiveness with levofloxacin alone as a second-line therapy (74% vs. 84%), although that study limited dosage to 750 mg/d and limited treatment time to 7 days (35). These rates are below the greater than 90% eradication rates for regimens with levofloxacin as first-line therapy used in countries like Italy and Holland (14-17, 36). Increased *H. pylori* resistance to quinolones has been shown in Belgium (16.8%), Italy (23.1%), and from 3% in 1999 to 15% in 2004 in France, Germany, and Spain (18, 19, 37-41). The October 2011 Maastricht IV -Florence consensus on treatment of *H. pylori* infections recommended standard triple therapy as first-line treatment in regions where the resistance of *H. pylori* to clarithromycin does not exceed 15% (42). In a recently published review of the role of quinolones in first-line therapy against *H. pylori* (43), the authors concluded that not all quinolones can be recommended as first-line therapy for eradicating *H. pylori*, although they can be considered as first-line therapy in specific situations primarily depending on local primary resistance to quinolones and macrolides. Studies also suggest trial implementation to assess the role of quinolones as first-line therapy.

Considering the ineffectiveness of standard therapies for eradicating *H. pylori* in our area, we evaluated treatment with levofloxacin and compared it to treatment with clarithromycin. We found an 89.3% eradication rate with LAO therapy using per protocol population analysis, and an 84.1% eradication rate using intention-to-treat analysis. This compares with 71.9% and 68.8% for CAO. The eradication rate for standard triple therapy with levofloxacin is higher than the recommended 80% rule. Since up to 60% of recent reports assessing triple therapy have failed to reach 80% *H. pylori* eradication using ITT, the eradication rate found in this study is better than expected (44).

No differences in adverse effects were found between the two lines of therapy. In addition the same number of patients (14 patients)discontinued treatment in each group. The most common adverse effects were nausea, vomiting, and epigastric pain in both treatment groups. A recent systematic review reported an 18% incidence of adverse events and a 3% incidence of serious adverse events which is consistent with our results (10). Finally, a recent meta-analysis showed a lower incidence of adverse effects with levofloxacin-based therapy combinations than with quadruple regimens (45).

Efforts should be directed towards finding first line treatments that ensure eradication rates over 90%. According to the recommendations of experts, quadruple regimens (primarily sequential and concomitant therapy) appear to be valuable alternative first-line therapies for obtaining higher eradication rates as well as for overcoming increasingly clarithromycin-resistant *H. pylori* (43, 44).

Our results of 84.1% of eradication rate by intention-to-treat analysis and 89.3% by protocol analysis for first-line *H. pylori* eradication therapy using the combination of levofloxacin, amoxicillin and PPIs for 10 days are encouraging. Other authors have reported favorable experiences with levofloxacin, but these studies have been evaluated it for second-line therapy, after one or more failed treatments (46). Other studies have evaluated the LAO regimen as first-line therapy with small numbers of patients (less than 50 patients), but with high eradication rates of 87% (16), 90% (13, 14), and 92% (15). First-line therapy with the

LAO scheme has been recommended for *H. pylori* eradication in areas where the primary resistance to levofloxacin is less than 10% (15). Although this resistance has not been measured in our environment, clarithromycin resistance is higher than 50% (22).

Although studies show that clarithromycin-based regimens achieve a higher rate of eradication in patients with peptic ulcers than in patients with functional dyspepsia (47, 48), the cure rate in our study was similar for both entities.

Triple therapy with the LAO regimen for 10 days represents a better alternative than does standard first-line therapy based on clarithromycin. The LAO regimen meets the proposed targets for *H. pylori* eradication of a greater than 80% eradication rate, simplicity (twice a day administration with excellent adhesion), and safety (few and mild side effects).

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