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-
uous 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* to this quinolone has been reported recently, and this could jeopardize its use in the future (18-20).

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 matches). 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 (\(^{13}\text{C}\)-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 \(^{13}\text{C}\)-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.**

<table>
<thead>
<tr>
<th></th>
<th>CAO (n=160)</th>
<th>LAO (n=157)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.7±11.5</td>
<td>47.8±14.2</td>
<td>0.346</td>
</tr>
<tr>
<td>Gender (male / female)</td>
<td>54/106</td>
<td>46/111</td>
<td>0.232</td>
</tr>
<tr>
<td>Diagnosis (NUD / peptic ulcer)</td>
<td>106 / 54</td>
<td>93 / 64</td>
<td>0.535</td>
</tr>
<tr>
<td>Gastritis (%)</td>
<td>106 (66.2)</td>
<td>93 (59.2)</td>
<td></td>
</tr>
<tr>
<td>Erosive gastritis (%)</td>
<td>32 (20)</td>
<td>37 (23.6)</td>
<td></td>
</tr>
<tr>
<td>Duodenal ulcers (%)</td>
<td>10 (6.2)</td>
<td>15 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Gastric ulcers (%)</td>
<td>12 (7.6)</td>
<td>12 (7.6)</td>
<td></td>
</tr>
<tr>
<td>(H.\ pylori) (scarce / abundant)</td>
<td>77 / 83</td>
<td>79 / 78</td>
<td>0.390</td>
</tr>
<tr>
<td>Breath test (not eradicated / eradicated) by intention-to-treat</td>
<td>50 / 110</td>
<td>25 / 132</td>
<td>0.001</td>
</tr>
<tr>
<td>Breath test (not eradicated / eradicated) by protocol</td>
<td>41 / 105</td>
<td>15 / 125</td>
<td>0.000</td>
</tr>
<tr>
<td>Adverse effects (YES / NO)</td>
<td>45 / 115</td>
<td>51 / 106</td>
<td>0.704</td>
</tr>
<tr>
<td>Intolerance (YES / NO)</td>
<td>14/146</td>
<td>17/140</td>
<td>0.332</td>
</tr>
<tr>
<td>Intestinal metaplasia (YES / NO)</td>
<td>24 / 136</td>
<td>26 / 131</td>
<td>0.410</td>
</tr>
<tr>
<td>Atrophy (YES / NO)</td>
<td>19 / 141</td>
<td>15 / 142</td>
<td>0.314</td>
</tr>
</tbody>
</table>

**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).
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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.

<table>
<thead>
<tr>
<th></th>
<th>CAO (n=160)</th>
<th>LAO (n=157)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori scarce</td>
<td>52/50</td>
<td>64/15</td>
<td></td>
</tr>
<tr>
<td>H. pylori abundant</td>
<td>58/25</td>
<td>68/10</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>110/50</td>
<td>132/25</td>
<td>0.440</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th></th>
<th>NUD (n=98)</th>
<th>UD (n=101)</th>
<th>Total (n=199)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori scarce</td>
<td>98/58</td>
<td>101/60</td>
<td>199/317</td>
<td>0.540</td>
</tr>
<tr>
<td>H. pylori abundant</td>
<td>199/118</td>
<td>317</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th></th>
<th>CAO (n=160)</th>
<th>LAO (n=157)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea &amp; Vomiting (%)</td>
<td>22 (13,8)</td>
<td>21 (13,4)</td>
<td></td>
</tr>
<tr>
<td>Epigastric pain (%)</td>
<td>20 (12,5)</td>
<td>27 (17,2)</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>4 (2,5)</td>
<td>11 (7,0)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>5 (3,1)</td>
<td>5 (3,2)</td>
<td></td>
</tr>
<tr>
<td>Rash (%)</td>
<td>2 (1,2)</td>
<td>1 (0,6)</td>
<td></td>
</tr>
<tr>
<td>Adverse effect total (%)</td>
<td>53 (33,1)</td>
<td>65 (41,4)</td>
<td>0.329</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th></th>
<th>CAO (n=160)</th>
<th>LAO (n=157)</th>
<th>Total (n=317)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastritis</td>
<td>75/31</td>
<td>78/15</td>
<td>209</td>
<td>0.69</td>
</tr>
<tr>
<td>Erosive gastritis</td>
<td>19/13</td>
<td>30/7</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>11/12</td>
<td>0/3</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>5/12</td>
<td>3/25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>110/50</td>
<td>132/25</td>
<td>317/0.439</td>
<td></td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th></th>
<th>NUD</th>
<th>UD</th>
<th>Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better</td>
<td>156</td>
<td>94</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>Same or worse</td>
<td>43</td>
<td>24</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>199</td>
<td>118</td>
<td>317</td>
<td>0.789</td>
</tr>
</tbody>
</table>

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 Levofoxacin, 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. However, Levofoxacin'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 levofoxacin 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 levofoxacin 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 levofoxacin 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 recom-
LAO scheme has been recommended for *H. pylori* eradication in areas where the primary resistance to levofl oxacin 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).

**REFERENCES**


