Comparison of amoxicillin and metronidazole effect on three-drug regimen for the treatment of *Helicobacter pylori* infection in children

**Abstract**

*Helicobacter pylori* is an important risk factor for chronic gastritis, peptic ulcer, and gastric cancer. Three-drug regimen is the first-line treatment for this infection, but the response rate to treatment varies in different geographical regions. This study was conducted to comparatively determine the effect of amoxicillin and metronidazole on three-drug regimen to treat *H. pylori* infection in 1–15-year-old children. This clinical trial was conducted on 82 patients aged 1–15 years with convenience sampling referring to the Endoscopy Unit of Hajar Hospital, Shahrekord. Group 1 was administered with clarithromycin, amoxicillin, and omeprazole (CAO), and Group 2 with, clarithromycin, metronidazole, and omeprazole (CMO). One month after completion of the treatment, stool antigen test was used to study the eradication of *H. pylori*. Data were analyzed using SPSS software by Chi-square test. Three of the 82 patients were excluded from the study because of side effects caused by drugs. Nearly 87.2% of the patients in CAO-treated group and 92.5% in CMO-treated group had response to treatment. There was no significant difference in eradication rate between the two regimens (\( P = 0.43 \)). The two regimens displayed no superiority over each other for eradicating *H. pylori* infection and response rate to treatment in children aged 1–15 years.

**Key words:** Amoxicillin, clarithromycin, *Helicobacter pylori*, metronidazole, omeprazole

**INTRODUCTION**

*Helicobacter pylori* is a spiral, Gram-negative, microaerophilic bacterium with polar flagella, which was first isolated from the end lining tissue of human stomach in 1982[1] *H. pylori* is a human stomach-specific pathogenic bacterium which has colonized in at least half of the whole population of the world.[2] Many studies have reported the decrease in the efficiency of this regimen because of increased resistance to clarithromycin and have recommended a new regimen to be introduced. However, this regimen remains to result in a good eradication in the regions with low prevalence of resistance to *H. pylori.[3]* We decided to compare the eradication rate of two three-drug regimens, clarithromycin, amoxicillin, and omeprazole (CAO) and clarithromycin, metronidazole, and omeprazole (CMO) for *H. pylori* infection to investigate their efficacy for *H. pylori* eradication in Chaharmahal and Bakhtiari province, southwest Iran.

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MATERIALS AND METHODS

This randomized clinical trial was conducted on 82 symptomatic patients with the following inclusion criteria: patients having symptoms (dyspepsia, epigastric pain, gastrointestinal bleeding, etc.) for 1 month to 2 years, not responding to outpatient treatment, and being 1–15 years old. The patients were admitted to the educational center of Hajar hospital, Shahrekord, Southwest Iran, for endoscopy. On performing endoscopy, we obtained two specimens from the patients’ gastric tissue. A specimen was used for rapid urease test (RUT) and the other one was sent to the laboratory for pathology examination using hematoxylin and eosin that is the only method that can detect other H. pylori-associated lesions (atrophy, intestinal metaplasia, etc.). In general, serologic assays cannot be used on their own in children and adolescents for either diagnosis of H. pylori infection or to monitor the success of therapy because the sensitivity and specificity for the detection of antibodies (IgG or IgA) against H. pylori in children vary widely. After 24 h, the results of RUT were prepared. All the patients with positive RUT result of gastric tissue biopsy specimens after 24 h or positive pathology results were included in the study. The exclusion criteria were patients with previous treatment for H. pylori infection, antibiotic therapy within 4 weeks prior to endoscopy, malignancy or suspected malignancy, gastrectomy, acquisition of severe hepatic disease or any severe diseases within the past 2 years, and having no compliance with the administered regimens. Patients fulfilling the therapy prerequisites were enrolled and informed about the research and related procedures. The patients were fully informed of the research purposes. Written consent was filled by all patients. Then, the patients enrolled were randomly assigned to two groups of 41 each, underwent treatment in one of the Groups of A or B. The patients in Group A were administered with CAO regimen and those in Group B were administered with CMO. The patients administered with CAO received 1–2 mg/kg omeprazole twice a day for 1 month, and simultaneously 50 mg/kg amoxicillin and 15 mg/kg clarithromycin twice a day for 2 weeks. The patients administered with CMO should receive 1 mg/kg omeprazole twice a day divided into two doses for 1 month and simultaneously 20 mg/kg metronidazole and 15 mg/kg clarithromycin twice a day for 2 weeks.

After the patients completed filling out checklists of the demographic data, they were informed of their next referring which was the date of the completion of regimens taking. The patients were told that they should inform the research team if any problems occur to them, particularly side effects or any other problems leading to the discontinuation of regimens taking. If a patient was not able to follow regimen for any reasons such as side effects, withdrawal from the study, and no tolerance, he/she was excluded from the study.

RESULTS

Overall, 82 patients were enrolled in this study, and three patients, two in CAO group and one in CMO group, were excluded from the study because of side effects. The two groups were matched by age and there was no significant difference in age between them [Table 1]. The data analysis indicated that there was no significant difference in H. pylori complete eradication between males and females in the two groups [Tables 2 and 3].

Furthermore, the findings indicated that the number of males and females with full eradication of H. pylori in the CAO- and CMO-treated groups was not significantly different [Tables 2 and 3].

Overall, the data analysis, irrespective of age and gender, indicated that the response rate was 87.2% for CAO regimen and 92.5% for CMO regimen with no significant difference in the eradication rate between the two regimens. Table 3 shows the comparison of the two studied regimens.

Regarding side effects, three patients exhibited intolerance to clarithromycin and no side effects were seen due to amoxicillin and metronidazole in this study. No difference was seen in side effects between the two groups.

DISCUSSION

Long-term single use of clarithromycin for respiratory tract diseases has caused increased resistance to it. Resistance to clarithromycin is the most important reason for failure of H. pylori treatment and decline in its eradication rate. The resistance rate to clarithromycin was obtained at 11.1%, 18.9%, and 29.3% in 2011 in Europe, Asia, and Americas, respectively. Several studies have found the decline in this regimen efficacy due to increased resistance to clarithromycin.

Metronidazole is used to treat anaerobic bacterial diseases, ameba, giardiasis, oral infections, and vaginosis and it has side effects including nausea, dyspepsia, pain, abdominal cramps, constipation, hairy tongue, glossitis, dry mouth, and bad taste, none of which were seen in the patients of the present study.
Under treatment with H. pylori infection

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number of individuals with H. pylori infection</th>
<th>Under treatment with CAO* regimen, n (%)</th>
<th>Under treatment with CMO** regimen, n (%)</th>
<th>P***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 5</td>
<td>Number of individuals with H. pylori infection</td>
<td>8 (80)</td>
<td>3 (100)</td>
<td>0.40</td>
</tr>
<tr>
<td>5-10</td>
<td>Number of individuals with H. pylori eradication</td>
<td>21 (95.5)</td>
<td>27 (96.4)</td>
<td>0.80</td>
</tr>
<tr>
<td>10-15</td>
<td>Number of individuals with H. pylori eradication</td>
<td>5 (71.4)</td>
<td>7 (77.8)</td>
<td>0.77</td>
</tr>
</tbody>
</table>
*CAO: Amoxicillin + clarithromycin + omeprazole-contained therapeutic regimen, **CMO: Metronidazole + clarithromycin + omeprazole-contained therapeutic regimen, ***P<0.05: The level of significance. H. pylori: Helicobacter pylori

Table 2: Eradication rate of Helicobacter pylori infection in both sexes between the two treatment groups

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number of individuals with H. pylori infection</th>
<th>Under treatment with CAO* regimen, n (%)</th>
<th>Under treatment with CMO** regimen, n (%)</th>
<th>P***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Number of individuals with H. pylori infection</td>
<td>15 (88.2)</td>
<td>20 (95.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>Female</td>
<td>Number of individuals with H. pylori eradication</td>
<td>19 (52.8)</td>
<td>17 (89.5)</td>
<td>0.76</td>
</tr>
</tbody>
</table>
*CAO: Amoxicillin + clarithromycin + omeprazole-contained therapeutic regimen, **CMO: Metronidazole + clarithromycin + omeprazole-contained therapeutic regimen, ***P<0.05: The level of significance. H. pylori: Helicobacter pylori

Table 3: Rate of eradication and response to Helicobacter pylori treatment in two groups

<table>
<thead>
<tr>
<th>Therapeutic regimen</th>
<th>Number of individuals with H. pylori eradication</th>
<th>Under treatment with CAO* regimen, n (%)</th>
<th>Under treatment with CMO** regimen, n (%)</th>
<th>P***</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAO*</td>
<td>Number of individuals with H. pylori eradication</td>
<td>34 (87.2)</td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>CMO**</td>
<td>Number of individuals with H. pylori eradication</td>
<td>37 (92.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
*CAO: Amoxicillin + clarithromycin + omeprazole-contained therapeutic regimen, **CMO: Metronidazole + clarithromycin + omeprazole-contained therapeutic regimen, ***P<0.05: The level of significance. H. pylori: Helicobacter pylori

Antelo et al. studied 120 patients assigned to three groups in Argentina. The eradication rate of the three regimens was reported to be similar, and the regimen administered for the Group 1 was offered as the best regimen because of fewer side effects. In a systematic review of 75 articles, the eradication rate of PPI + amoxicillin + clarithromycin and PPI + metronidazole + clarithromycin regimens was 83.5% and 68.6%, respectively. All the three regimens were administered for 14 days, which could be due to the difference in the studied geographical regions and high prevalence of resistance to metronidazole in these regions.

Moreover, a study by Paoluzi et al. in 2006 in Italy on 486 patients to compare 1- and 2-week three-drug regimens concluded that the eradication rate of the 2-week treatment was much higher than the 1-week treatment, and the eradication rate of amoxicillin-contained three-drug regimen was much higher than that of metronidazole-contained one (70% and 52%, respectively), which is lower than the eradication rate obtained for both regimens in the present study. This could be explained by high resistance to clarithromycin and metronidazole in the area of study.

In a systematic review in Iran, H. pylori resistance to metronidazole, clarithromycin, amoxicillin, was 61.6%, 22.4%, and 16.0%, respectively. In Khadem study in Isfahan, Iran, H. pylori resistance to clarithromycin, metronidazole, and amoxicillin was 15.3%, 55.1%, and 6.4%, respectively.

Inconsistent with the present study, a study by Kutluk et al. reported only 50% of eradication rate in children of 2–15 years of age for CAO. A study in China found 66.4% eradication rate for CAO in children, and a study in Turkey obtained the eradication rate of 64.4%. Culture and sensitivity tests were not conducted in this study that can be considered a limitation of this study.

**CONCLUSION**

The comparison of two therapeutic regimens, CAO and CMO, indicated no significant difference in complete...
recovery and *H. pylori* eradication between the two regimens. The side effects were approximately similar in the two studied groups. Therefore, both regimens could be used to eliminate *H. pylori* infection and treat the patients with such infection.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**