Comparison of standard and standard plus vitamin E therapy for Helicobacter pylori eradictions in children

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ABSTRACT

Background/Aims: Although various drugs can be used in adults for Helicobacter pylori eradication in adults, treatment options are limited in children. The aim of this study was to compare the effects of the standard lansoprazole, amoxicillin, and clarithromycin (LAC) protocol to those of LAC + vitamin E (LACE) combination for H. pylori eradication.

Materials and Methods: The study included 90 children (age range: 10-17 years) who were admitted to four pediatric gastroenterology centers between March 2011 and November 2012 with dyspeptic symptoms and who had tested positive for H. pylori by 14C-urea breath tests. The patients were randomized into two groups. The LAC group (45 patients (pts)) was treated with a standard regimen consisting of lansoprazole (1 mg/kg/day), amoxicillin (50 mg/kg/day), and clarithromycin (14 mg/kg/day), each of which was given in two equally divided doses every 12 h for 14 days; the LACE group (45 pts) was given the standard regimen and vitamin E at 200 IU/day for 14 days. H. pylori eradication was assessed using the 14C-UBT in the 6th week after the cessation of treatment.

Results: H. pylori was eradicated in 21 (46.6%) pts in the LAC group, while it was eradicated in 29 (64.4%) pts in the LACE group. There was no statistical difference between the two groups (p=0.13).

Conclusion: The eradication rate of H. pylori in children while using the LAC regimen has decreased in the last years. The LACE regimen has been associated with an increased eradication rate but can reach to statistically significance. Further studies with larger cohorts are needed to examine the success of the LACE regimen for H. pylori eradication.

Keywords: H. pylori, children, eradication, vitamin E

INTRODUCTION

Infection with Helicobacter pylori occurs most commonly in early childhood, both in industrialized and developing countries. Many features of these infections such as prevalence, clinical presentation and complications, diagnostic methods, and antibiotic resistance are age-specific and differ from those in adults (1). The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) suggested the same guidelines for first-line therapy such as triple therapy with a proton pump inhibitor (PPI) and amoxicillin and imidazole or clarithromycin; therapy with bismuth salts, amoxicillin, and imidazole; or sequential therapy (2). An important factor that can limit treatment success is antibiotic resistance, which varies among countries; therefore, the surveillance of antibiotic resistance rates in different geographic areas is recommended. In particular, clarithromycin and metronidazole resistances have some regional differences (1,3). In Turkey, metronidazole resistance has the highest frequency (36.4%) in children, followed by clarithromycin resistance (18.2%-25.7%) (4,5). A 10-year epidemiological analysis (1996-2005) in the Turkish population reported a gradual decrease in eradication success from 80% to 60% while using a PPI, amoxicillin, and clarithromycin (6). The increasing number of children infected with resistant H. pylori strains encourages the evaluation of new treatment protocols (1).
Although various drug combinations can be used in adults for *H. pylori* eradication, treatment options are limited in children. In some studies conducted in adults, it has been shown that antioxidant treatments can be effective for eradication of *H. pylori*. Sezikli et al suggested that *H. pylori* intensity and neutrophilic activity decreased after increasing gastric ascorbic acid and α-tocopherol concentrations; this suggested that supplementation with vitamins C and E could increase the eradication rates by impairing the microenvironment created by the bacteria and facilitating the diffusion of antibiotics into the gastric mucosa (7,8). Calvino-Fernandez et al suggested that treating infected cells with vitamin E prevented increases in intracellular reactive oxygen species (ROS) and mitochondrial damage; these findings were consistent with observations from another study which stated that *H. pylori* induced a mitochondrial ROS-mediated programmed cell death pathway (9).

The mechanism by which dietary supplementation with antioxidant micronutrients interferes with *H. pylori* infection and associated diseases is unclear (10). In some studies conducted in adults, it has been shown that antioxidant treatments can be effective in the eradication of *H. pylori*. In the literature, there has been no study regarding the effect of antioxidant treatments on *H. pylori* eradication in children. The aim of this study was to compare the standard lansoprazole, amoxicillin, and clarithromycin (LAC) protocol to the LAC + vitamin E (LACE) combination for the eradication of *H. pylori*.

**MATERIALS AND METHODS**

Between March 2011 and November 2012, 100 children (age range: 10-17 years), who had been admitted to four pediatric gastroenterology centers in Turkey because of dyspeptic complaints (stomach ache, bloating, and nausea) and who had tested positive for *H. pylori* with the 14C-urea breath test (UBT) were examined prospectively. After informing parents about the procedures, informed consents were obtained. Participants were excluded based on the following criteria: (1) age <10 years or > 18 years, (2) a significant underlying disease including liver, cardiac, pulmonary, and renal diseases, neoplasia, or coagulopathy, (3) history of gastric surgery, (4) glucose-6-phosphate deficiency, and (5) previous history of allergic reactions to any of the medications used in this protocol. 8 cases did not come for the control after the treatment. Two cases were omitted from the study because of the side effects of the drugs; the study was completed in a total of 90 cases.

The mean age of the patients was 13.1±2.2 years (range: 10-17 years). Sixty-six (73%) of them were female, and 24 (27%) of them were male. Endoscopy was performed in all cases using a Pentax EG-2730K gastroscope (Pentax, Tokyo, Japan). None of the patients had taken any medications for *H. pylori* eradication. The *H. pylori* (+) patients were randomized into two groups. The LAC group (47 patients (pts)) received the standard regimen that consisted of lansoprazole (1 mg/kg/day), amoxicillin (50 mg/kg/day), and clarithromycin (14 mg/kg/day), each given in two equally divided doses every 12 h for 14 days, and the LACE group (45 pts) received the standard regimen and vitamin E (200 IU/day) for 14 days.

Mild to moderate adverse events were reported by two patients in the LAC group, including nausea (4%), headache (2%), and vomiting (4%), and by three patients in the LACE group, including abdominal pain (4%) and diarrhea (2%). The LAC group treatment had to be discontinued only in two cases in because of severe headache and vomiting.

No antibiotics, PPIs, or *H₂*-receptor blockers were allowed prior to the control eradication test. *H. pylori* eradication was assessed by a 14C-UBT in the 6th week after cessation of treatment. To carry out the 14C-UBT, the patient swallowed a 14C-labeled urea-containing capsule (Helicap, Institute of Isotopes, Budapest, Hungary) with water after an overnight fast. The overall activity of these capsules was as small as 1 μCi (37 KBq). After 15 min, the patient exhaled into a dry cartridge (Heliprobe breath card, Kibion AB, Uppsala, Sweden) through its mouthpiece until the color of the card indicator changed from orange to yellow, which took about 1-2 mins. Finally, the test results were expressed on the LCD of the analyzer in a numeric fashion (0: patient not infected, 1: borderline result, or 2: patient infected); these scores corresponded to radioactivity as count per minute (CPM): <25 CPM: patient not infected, 25-50 CPM: borderline result, and >50 CPM: patient infected. We considered grades 0 and 1 as negative results for our study, and only samples with activities that were more than 50 CPM were regarded as positive (11,12).

**Statistical analysis**

Besides the standard descriptive statistical calculations (mean, median, and standard deviation), the Chi square test was used in the evaluation of qualitative data. For the average comparison of the two groups, Student t-test and Cross tables were used. The statistical significance level was established at p<0.05.

**RESULTS**

The age and sex distribution of the patients were similar in the groups (Table 1).

Abdominal pain was the most common symptom in the group 1 and group 2 (100% and 95%, respectively). There was no statistical difference between the two groups in regards of symptoms (Table 2).

Upper gastrointestinal system endoscopy was performed in the 90 cases. Antral gastritis was found in 66 patients (73%)
and pan-gastritis in 24 patients (27%). Four of the patients with antral gastritis had peptic ulcers (Table 3). Histopathological evaluation of the gastric biopsies of the patients was all positive for *H. pylori* gastritis.

*H. pylori* was eradicated in 21 (46.6%) patients in the LAC group, whereas it was eradicated in 29 (64.4%) patients in the LACE group. There was no statistical difference between the two groups (p=0.13) (Figure 1). Two patients in the LAC group and three patients in the LACE group developed adverse drug reactions. All of these reactions were minor gastrointestinal reactions (nausea, vomiting, and diarrhea). Treatment had to be discontinued because of severe headache and vomiting in only two cases in the LAC group.

**DISCUSSION**

*H. pylori* is a gram negative bacterium that infects the human stomach and affects approximately half of the world’s population. In Europe and North America, the epidemiology of *H. pylori* infection in children has changed in recent decades. Low incidence rates have been found in the northern and western European countries, resulting in a prevalence far below 10% in children and adolescents. In contrast, the infection is still common in certain geographic areas such as southern or eastern Europe, Mexico, and certain immigrant populations from South America, Africa, most Asian countries, and the aboriginal people in North America (2). The prevalence of *H. pylori* among children has been reported to be 6.5%-31.6% in Europe (13-15), whereas the prevalence of *H. pylori* among children has been reported to be 53%-66.3% in Turkey (16-19). Therefore, *H. pylori* is still a major problem in Turkey. The current standard first-line treatment to eradicate *H. pylori* is a triple therapy (LAC) combining a proton-pump inhibitor (PPI, double dose) with two antibiotics, mainly clarithromycin (500 mg b.i.d.) and amoxicillin (1 g b.i.d.) or metronidazole (500 mg b.i.d.), which was prescribed according to worldwide guidelines, including the Maastricht III Consensus Report (20-22). Today, these therapies have been recommended as the first choice in the ESPGHAN and NASPGHAN guidelines (2). However, reports have demonstrated a gradual decrease in the rate of successful eradication with LAC protocol (1,3,5,23). For this reason, different treatment modalities have been developed in adults; unfortunately, treatment options remain limited for children.

Trace minerals and vitamins are essential for life. They act as essential cofactors of various enzymes and as organizers of the molecular structures of the cell. The major active form of vitamin E in the human body, α-tocopherol, accounts for 95% and is the most effective lipid-soluble anti-oxidant in biomembranes (24). Taking vitamin E levels at higher than the required amounts has not shown any negative effects because vitamin E is not stored like other lipo-soluble vitamins. If vitamin E is taken in higher amounts, in a few days, it will be removed from the body by the excrement and/or urine.

There have been numerous studies that have evaluated the effects of vitamin E on gastric mucosa in the literature. It has been reported that α-tocopherol could ameliorate the aggravation of stress-associated gastric mucosal damage (25). In in vivo assays, the consumption of vitamins C and E could reduce the gastric *H. pylori* loads in animal models (26-29). Sies et al. (30) showed that the concentrations of α-tocopherol in *H. pylori*-negative subjects were higher in the corpus than in the antrum or duodenum. Sugimoto et al. (31) showed that vitamin E has a protective effect on gastric mucosal injury induced by *H. pylori* infection in gerbils; it induces this effect by inhibiting the accumulation of activated neutrophils. Sezikli et al. (32) showed that adding the prescribed doses of vitamins E and C to antimicrobial therapy was effective in eradicating *H. pylori* infection in adults. Epidemiological studies have reported that high-dose vitamin E and vitamin C intake reduced the risk of gastric cancer. Jun-Ling Ma et al. detected that garlic and vitamin treatments were associated with non-statistically significant reductions in gastric cancer incidence and mortality and that vitamin treatment was associated with

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**Table 2. Symptoms of the patients**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>LAC group (n=45)</th>
<th>LACE group (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>45 (100%)</td>
<td>43 (95%)</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>33 (73%)</td>
<td>21 (46%)</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>28 (62%)</td>
<td>21 (46%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>27 (60%)</td>
<td>32 (71%)</td>
</tr>
<tr>
<td>Pyrosis</td>
<td>23 (51%)</td>
<td>17 (37%)</td>
</tr>
<tr>
<td>Awakening from sleep with stomach pain</td>
<td>17 (37%)</td>
<td>17 (37%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>17 (37%)</td>
<td>10 (22%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 (29%)</td>
<td>8 (17%)</td>
</tr>
</tbody>
</table>

**Table 3. Results of the upper gastrointestinal system endoscopy of the patients**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>LAC group (n=45)</th>
<th>LACE group (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antral gastritis</td>
<td>33 (73%)</td>
<td>33 (73%)</td>
</tr>
<tr>
<td>Pangastritis</td>
<td>12 (27%)</td>
<td>12 (27%)</td>
</tr>
<tr>
<td>Peptic Ulcers</td>
<td>1 (3%)</td>
<td>3 (7%)</td>
</tr>
</tbody>
</table>

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**Figure 1. The eradication rate of *H. pylori***
a statistically significant number of fewer deaths from gastric or esophageal cancer, which was a secondary endpoint (33). Persson et al. (34) suggested that those who had very low plasma levels of a-carotene and b-carotene were at higher risk of gastric cancer.

However, some meta-analyses and publications have shown that these antioxidant treatments do not have any effects on *H. pylori* eradication. Li et al showed that adding vitamin C and/or E supplements to the *H. pylori* eradication regimen did not improve the eradication rate. However, they reported that the reason for this may be the small sample size and the low-to-moderate methodological quality (35). In another study, vitamin E had no effect on *H. pylori* growth compared to that of controls. Chatterjee et al suggested that some antioxidants such as vitamin C, garcinol, and protykin, but not vitamin E, have potential as antimicrobial agents against *H. pylori* (36).

In the literature, there have been no studies about the effect of antioxidant treatments on the eradication of *H. pylori* in children. In our study, eradication rates were higher in the LACE group than in the LAC group, but there was no statistical difference between the two groups. These findings may be associated with the small size of the study group. In addition, the dose of and the duration of vitamin E administered may have been inadequate for the eradication of *H. pylori* because the exact dose and duration of vitamin E in combination with the LAC regimen has not been clearly defined.

In conclusion, the eradication rate of *H. pylori* with the LAC regimen has decreased in the last years. The LACE regimen has been associated with an increased eradication rate but can reach to statistically significance. Further studies with larger cohorts are needed in order to examine the success of the LACE regimen for *H. pylori* eradication.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**REFERENCES**


