Turk J Gastroenterol *2014; 25 (Suppl.-1): 99-103*

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

Gökhan Tümgör[1], Masallah Baran[2], Murat Çakır[3], Hasan Ali Yüksekkaya[4], Sema Aydoğdu[5]
[1]Department of Pediatric Gastroenterology, Çukurova University Faculty of Medicine, Adana, Turkey
[2]Department of Pediatric Gastroenterology, Tepecik Training and Research Hospital, İzmir, Turkey
[3]Department of Pediatric Gastroenterology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey
[4]Department of Pediatric Gastroenterology, Necmettin Erbakan University Faculty of Medicine, Konya, Turkey
[5]Department of Pediatric Gastroenterology, Ege University Faculty of Medicine, İzmir, Turkey

Original Article

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).

Address for Correspondence: Gökhan Tümgör, Department of Pediatric Gastroenterology, Çukurova University Faculty of Medicine, Adana, Turkey
E-mail: gtumgor74@yahoo.com
Received: May 21, 2013 **Accepted:** September 30, 2013
 • Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2014.5592

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 H_2-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 ^{14}C-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%)

Table 1. Age and sex distrubution of the patients

	LAC group (n=45)	LACE group (n=45)	p
Age (year)	13.5±2.2 (10-17)	12.8±2.2 (10-17)	0.9
Sex (F/M)	35/10	31/14	0.47

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.

Table 2. Symptoms of the patients

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

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

	LACE group (n=45)	LAC group (n=45)
Antral gastritis	33 (73%)	33 (73%)
Pangastritis	12 (27%)	12 (27%)
Peptic Ulcers	1 (3%)	3 (7%)

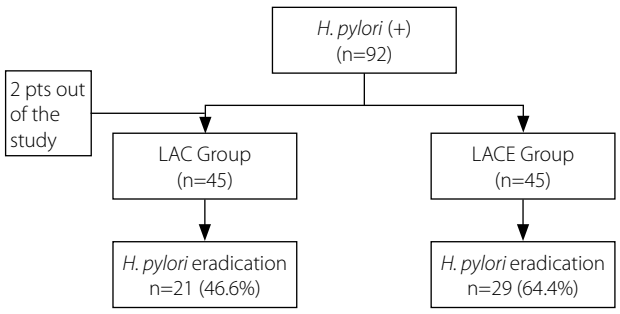

Figure 1. The eradication rate of *H. pylori*.

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

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

1. Homan M, Hojsak I, Kolacek S. Helicobacter pylori in Pediatrics. Helicobacter 2012; 17 (Suppl 1): 43-8.
2. Koletzko S, Jones NL, Goodman KJ, et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr 2011; 53: 230-43.
3. Gerrits MM, van Vilet Arnoud HM, Kuipers EJ, et al. Helicobacter pylori and antimicrobial resistance: molecular mechanisms and clinical implications. Lancet Infect Dis 2006; 6: 699-709.
4. Ozcay F, Kocak N, Temizel IN, et al. Helicobacter pylori infection in Turkish children: comparison of diagnostic tests, evaluation of eradication rate, and changes in symptoms after eradication. Helicobacter 2004; 9: 242-8.
5. Erdur B, Ozturk Y, Gurbuz ED, Yilmaz O. Comparison of Sequential and Standard Therapy for Helicobacter pylori Eradication in Children and Investigation of Clarithromycin Resistance. J Pediatr Gastroenterol Nutr 2012; 55: 530-3.
6. Kadayifci A, Buyukhatipoglu H, Cemil Savas M, Simsek I. Eradication of Hp with triple therapy: an epidemiologic analysis of trends in Turkey over 10 years. Clin Ther 2006; 28: 1960-6.
7. Sugimoto N, Yoshida N, Nakamura Y, et al. Influence of vitamin E on gastric mucosal injury induced by Helicobacter pylori infection. Biofactors 2006; 28: 9-19.
8. Sezikli M, Cetinkaya ZA, Guzelbulut F, et al. Effects of Alpha Tocopherol and Ascorbic Acid on Helicobacter pylori Colonization and the Severity of Gastric Inflammation. Helicobacter 2012; 17: 127-32.
9. Calvino-Fernández M, Benito-Martínez S, Parra-Cid T. Oxidative stress by Helicobacter pylori causes apoptosis through mitochondrial pathway in gastric epithelial cells. Apoptosis 2008; 13: 1267-80.
10. Sun YQ, Girgensone I, Leanderson P, Petersson F, Borch K. Effects of Antioxidant Vitamin Supplements on Helicobacter pylori-induced Gastritis in Mongolian Gerbils. Helicobacter 2005; 10: 33-42.
11. Megraud F. European Paediatric Task Force on Helicobacter pylori. Comparison of non-invasive tests to detect Helicobacter pylori infection in children and adolescents: results of a multicenter European study. J Pediatr 2005; 146: 198-203.
12. Ghanaei FM, Sanaei O, Joukar F. Clinical validation of an office-based 14c-ubt (heliprobe) for h. pylori diagnosis in iranian dyspeptic patients. gastroenterology research and practice, 2011; 1-5.
13. Bauer S, Krumbiegel P, Richter M, et al. Influence of sociodemographic factors on Helicobacter pylori prevalence variability among schoolchildren in Leipzig, Germany. A long-term follow-up study. Cent Eur J Public Health 2011; 19: 42-5.
14. den Hoed CM, Vila AJ, Holster IL, et al. Helicobacter pylori and the birth cohort effect: evidence for stabilized colonization rates in childhood. Helicobacter 2011; 16: 405-9.
15. Oleastro M, Pelerito A, Nogueira P, et al. Prevalence and incidence of Helicobacter pylori Infection in a healthy pediatric population in the Lisbon area. Helicobacter 2011; 16: 363-72.
16. Ceylan A, Kirimi E, Tuncer O, Turkdoğan K, Ariyuca S, Ceylan N. Prevalence of Helicobacter pylori in children and their family members in a district in Turkey. J Health Popul Nutr 2007; 25: 422-7.
17. Altuglu I, Sayiner AA, Ozacar T, Egemen A, Bilgic A. Seroprevalence of Helicobacter pylori in a pediatric population. Turk J Pediatr 2001; 43: 125-7.
18. Selimoglu MA, Ertekin V, Inandi T. Seroepidemiology of Helicobacter pylori infection in children living in eastern Turkey. Pediatr Int 2002; 44: 666-9.
19. Ozden A, Bozdayi G, Ozkan M, Kose KS. Changes in the seroepidemiological pattern of Helicobacter pylori infection over the last 10 years in Turkey. Turk J Gastroenterol 2004; 15: 156-8.
20. Malfertheiner P, Megraud F, O'Morain C, et al. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. Gut 2007; 56: 772-81.
21. Lam SK, Talley NJ. Report of the 1997 Asia Pacific Consensus on the management of Helicobacter pylori infection. J Gastroenterol Hepatol 1998; 13: 1-12.
22. Bourke B, Ceponis P, Chiba N, et al. Canadian Helicobacter Study Group Consensus Conference: Update on the approach to Helicobacter pylori infection in children and adolescents-an evidence-based evaluation. Can J Gastroenterol 2005; 19: 399- 408.

23. Tepes B, O'Connor A, Gisbert JP, O'Morain C. Treatment of Helicobacter pylori infection 2012 Helicobacter 17 (Suppl 1): 36-42.
24. Akçam M. Helicobacter pylori and Micronutrients. Indian Pediatrics; 2010: 47: 119-26.
25. Oh TY, Yeo M, Han SU, et al. Synergism of Helicobacter pylori infection and stress on the augmentation of gastric mucosal damage and its prevention with alpha-tocopherol. Free Radic Biol Med 2005; 38: 1447-57.
26. Zhang HM, Wakisaka N, Maeda O, Yamamato T. Vitamin C inhibits the growth of a bacterial risk factor for gastric carcinoma: Helicobacter pylori. Cancer 1997; 80: 1897-902.
27. Wang X, Wille´n R & Wadstro¨m T. Astaxanthin-rich algal meal and vitamin C inhibit Helicobacter pylori infection in BALB/cA mice. Antimicrob Agents Chemother 2000; 44: 2452-7.
28. Sjunnesson H, Sturegard E, Willen R, Wadström T. High intake of selenium, beta-carotene, and vitamins A, C, and E reduces growth of Helicobacter pylori in the guinea pig. Comp Med 2001; 51: 418-23.
29. Sun YQ, Girgensone I, Leanderson P, Petersson F, Borch K. Effects of antioxidant vitamin supplements on Helicobacter pylori induced gastritis in Mongolian gerbils. Helicobacter 2005; 10, 33-42.
30. Sies H, Stahl W. Vitamins E and C, beta-carotene,and other carotenoids as antioxidants. Am J Clin Nutr 1995; 62 Suppl 6: 1315-21.
31. Sugimoto N, Yoshida N, Nakamura Y, et al. Influence of vitamin E on gastric mucosal injury induced by Helicobacter pylori infection. Biofactors 2006; 28: 9-19.
32. Sezikli M, Cetinkaya ZA, Sezikli H, et al. Oxidative Stress in Helicobacter pylori Infection: Does Supplementation with Vitamins C and E Increase the Eradication Rate? Helicobacter 2009; 14: 280-5.
33. Ma JL, Zhang L, Brown LM, et al. Fifteen-Year Effects of Helicobacter pylori, Garlic, and Vitamin Treatments on Gastric Cancer Incidence and Mortality J Natl Cancer Inst 2012; 104: 488-92.
34. Persson C, Sasazuki S, Inoue M, et al and for the JPHC Study Group. Plasma levels of carotenoids, retinol and tocopherol and the risk of gastric cancer in Japan: a nested case-control study. Carcinogenesis 2008; 29: 1042-8.
35. Li G, Li L, Yu C, Chen L. Effect of vitamins C and E supplementation on Helicobacter pylori eradication: a meta-analysis. Br J Nutr 2011; 106: 1632-7.
36. Chatterjee A, Bagchi D, Yasmin T, Stohs SJ. Antimicrobial effects of antioxidants with and without clarithromycin on Helicobacter pylori. Mol Cell Biochem 2005; 270: 125-30.