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Influence of vitamin C and E supplementation on the eradication rates of triple and quadruple eradication regimens for *Helicobacter pylori* infection

STOMACH

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ABSTRACT

Background/Aims: In our study, we aimed to assess the effect of vitamin E and C supplementation to triple and quadruple *Helicobacter pylori* eradication regimens.

Materials and Methods: Four hundred patients with *H. pylori* infection were classified into four groups. Patients in group A (n=100) received amoxicillin, clarithromycin, and lansoprazole for 2 weeks. In group B, patients (n=100) received vitamins C and E for a month, in addition to amoxicillin, clarithromycin, and lansoprazole for 2 weeks. Patients in group C (n=100) received amoxicillin, clarithromycin, lansoprazole, and bismuth subcitrate for 2 weeks, whereas those in group D (n=100) received vitamins C and E for a month, in addition to amoxicillin, clarithromycin, lansoprazole, and bismuth subcitrate for 2 weeks. *H. pylori* eradication was assessed with the C14 urea breath test 2 months after the end of the therapy. The eradication rate was assessed using per-protocol (PP) and intention-to-treat (ITT) analyses.

Results: Three hundred forty-eight patients finished the study. The eradication of *H. pylori* was achieved in 63 of 84 patients (75%) by PP and 63 of 100 (63%) by ITT analysis in group A, 60 of 84 (71.4%) by PP and 60 of 100 (60%) by ITT analysis in group B, 72 of 89 (80.9 %) by PP and 72 of 100 (72%) by ITT analysis in group C, and 76 of 91 (83.5%) by PP and 76 of 100 (76%) by ITT analysis in group D. There was no remarkable change between groups A and B (p>0.05). Similar results were also found between groups D and C (p>0.05).

Conclusion: This study revealed that supplementing vitamins C and E to either the triple or quadruple therapies did not provide an additional advantage for achieving significantly higher eradication rates for *H. pylori*.

Keywords: *Helicobacter pylori*, eradication rate, bismuth subcitrate, vitamins E and C

INTRODUCTION

Helicobacter pylori infection is more prevalent in adults worldwide, mostly in less developed countries (1). *H. pylori* colonizes various areas of the stomach (2,3) and may lead to the occurrence of non-specific symptoms such as burning abdominal pain, nausea, vomiting, bloating, burping, loss of appetite, and weight loss (4,5). Mostly, people infected by *H. pylori* have no symptoms, and they do not develop *serious* health *problems such* as and peptic ulcers gastric cancer (6). For detecting *H. pylori* infection in patients who suffer from the symptoms of dyspepsia, invasive (biopsy check during upper endoscopy with a histopathological examination and rapid urease test) and non-invasive [carbon urea breath test (UBT), fecal antigen test, blood antibody test, and urine enzyme-linked immune sorbent assay test] tests are used (7). Treatment for *H. pylori* eradication is recommended in case of conditions related to *H. pylori* infection such as mucosa-associated lymphoid tissue lymphoma, pre-cancerous lesions (multifocal atrophic lesions, metaplasia, and dysplasia), peptic ulcer disease, atrophic gastritis, gastric resection due to early cancer, in patients having gastric cancer in their family, and in certain cases of dyspepsia (8).

Triple therapy with amoxicillin (AMPC), clarithromycin (CAM) or metronidazole, and proton pump inhibitor (PPI) has been used in the initial step for the treatment of *H. pylori* infection with eradication rates of over 80%

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in developed countries (8-10) in spite of reports that reveal the decreasing effectivity of triple therapies in developing countries (11,12). Another option for *H. pylori* eradication is quadruple therapy, which is a bismuth-based regimen with PPI and two antibiotics (13). Unfortunately, bismuth-based quadruple therapy seems to be far from satisfying the expectations of being more efficient in the eradication of *H. pylori* when compared with that by the triple therapy (14). Additionally, vitamins C and E, as antioxidants, have been investigated to display their effect in the eradication of *H. pylori* infection (15,16). It has been thought that vitamins C and E break the microenvironment created by *H. pylori* or directly inhibit bacteria. In some studies, the disadvantages of antioxidants on *H. pylori* colonization and proliferation have been shown (17-19).

In our study, we aimed to assess the improvement in the *H. pylori* eradication rate when vitamin E and C supplementation was used together with the standard therapies.

MATERIALS AND METHODS

Four hundred patients with *H. pylori* positive non-ulcer dyspepsia were included in this retrospective study. The patients were randomly divided into four groups. Patients in group A (n=100) received triple therapy with amoxicillin (1 g, b.i.d.), clarithromycin (500 mg, b.i.d.), and lansoprazole (30 mg, b.i.d.), for 14 days. In group B, patients (n=100) received oral vitamin C (500 mg/day) and oral vitamin E (100 U/day) for 30 days, in addition to amoxicillin (1 g, b.i.d.), clarithromycin (500 mg, b.i.d.), and lansoprazole (30 mg, b.i.d.) for 14 days. Patients in group C (n=100) received quadruple therapy with amoxicillin (1 g, b.i.d.), clarithromycin (500 mg, b.i.d.), lansoprazole (30 mg, b.i.d.), and bismuth subcitrate (400 mg, b.i.d.) for 14 days. In group D, patients (n=100) received oral vitamin C (500 mg/day) and oral vitamin E (100 U/day) for 30 days, in addition to amoxicillin (1 g, b.i.d.), clarithromycin (500 mg, b.i.d.), lansoprazole (30 mg, b.i.d.), and bismuth subcitrate (400 mg, b.i.d.) for 14 days (Figure 1). All patients underwent baseline evaluation including blood laboratory tests, detailed medical history assessment, and physical examination. In this study, for all patients with non-ulcer dyspepsia, *H. pylori* infection was examined by a rapid urease test (Grupobios product, Chile), and a histopathological evaluation was performed. At least two biopsy specimens were taken from the gastric mucosa for histopathological evaluation, and the rapid urease test was performed during the esophagogastroduodenoscopy. Patients were enrolled in the study after the identification of *H. pylori* as a result of both tests. The eradication rate of *H. pylori* was determined by UBT at least 2 months after the end of the treatment. A negative UBT result was described as successful eradication. Compliance and adverse events (i.e., nausea, vomiting and diarrhea) of the treatment were determined by a personal interview after the completion of the therapy. Therapy compliance was considered in patients who reported that they took more than 80% of the tablets. The unsuccessful eradication of *H. pylori* as well as the violation of protocol was considered as treatment deficit.

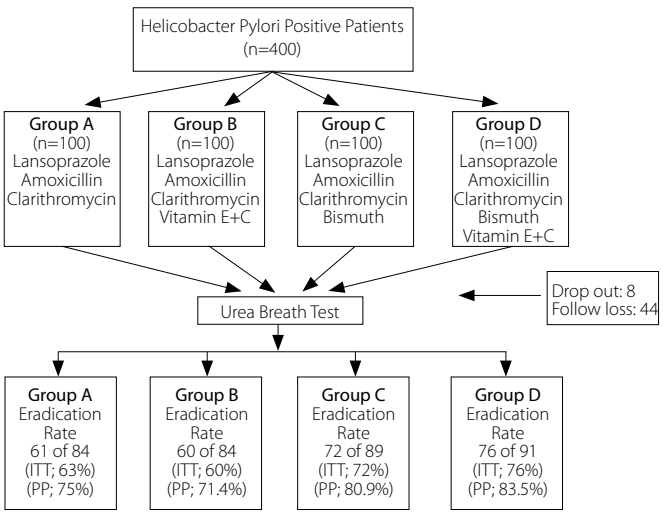

Figure 1. Flow chart of our study

The exclusion criteria for our patients were those with a history of gastric cancer or surgery, treatment of *H. pylori*, deteriorated renal or liver function, pregnancy, and allergy to antibiotics. Patients who had been treated with bismuth, PPIs, H_2 receptor blockers, or antibiotics within the previous month were also excluded to avoid interference with the eradication of *H. pylori*. Our study protocol conforms to the Helsinki declaration. Written informed consents were obtained from all individuals enrolled in our study.

Statistical Analysis

The overall eradication rates were assessed with per-protocol (PP) and intention-to-treat (ITT) analyses. Statistical analyses were conducted with SPSS 19.0 software (SPSS; Chicago, Illinois, USA). Shapiro–Wilk test was used for the distribution of the data. Continuous variables were defined as standard deviation or median (min–max), and categorical variables were expressed as percentage and frequency. Pearson chi-square test was used to determine the difference between groups for the categorical variables. The continuous variables were compared by independent sample t-test or Mann–Whitney U test for two groups. Kruskal–Wallis test was used to determine the differences between the four groups. *A p*-value of less than 0.05 was considered to be statistically significant for the tests.

RESULTS

In this retrospective study, 400 *H. pylori*-positive patients received triple (lansoprazole, amoxicillin, and clarithromycin) or quadruple (triple therapy plus bismuth subcitrate) eradication regimens with/without vitamin C and E supplementation. A total of 348 patients finished the study. Forty four patients did not visit our clinic after treatment, and 8 patients left the study due to side effect (5 patients reported diarrhea and 3 reported nausea and vomiting). Clinical and demographic features of our patients are shown in Table 1. There were no statistically remarkable changes in terms of gender and age (p=0.556 and

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p=0.051, respectively) between groups. *H. pylori* eradication was observed in 84 of 150 smokers (56%) and in 187 of 198 non-smokers (94.4%). The success rate of *H. pylori* eradication in smokers was significantly lower than that in non-smokers (p<0.001).

Considering the patients who completed the study, the eradication *of H. pylori* was achieved in 61 of 84 patients in group A (ITT, 63%; PP, 75%), 60 of 84 in group B (ITT, 60%; PP, 71.4%), 72 of 89 in group C (ITT, 72%; PP, 80.9%) and 76 of 91 in group D (ITT, 76%; PP, 83.5%) (Table 2). Group D was chosen for comparison with the others because of the most effective medication content. Comparative analysis for the eradication rates of *H. pylori* was assessed by PP and ITT analyses. While the PP comparison of group D with that of group A, B, and C results were p=0.228, p=0.082, and p=0.792, the ITT results were p=0.046, p=0.015, and p=0.519, respectively.

Although, vitamin C and E supplementation were added to the triple and quadruple therapy in groups B and D, respectively, it was observed that there were no significant change between groups A and B (PP, p=0.728 and ITT, p=0.663) and also between groups C and D (PP, p=0.792 and ITT, p=0.519). Adding vitamins E and C to the triple or quadruple therapy for *H. pylori* eradication seemed to be statistically insignificant.

DISCUSSION

The differences of the success rates of the treatment protocols to cure *H. pylori* infection mostly depend on antibiotic resistance and poor compliance. Additionally, factors including age, smoking habits, alcohol consumption, diet, gene polymorphisms, and drug sensitivity are thought to be effective on *H. pylori* eradication rates (9,13).

Table 1. Demographics and clinical variables of groups

	Group A (n=100)	Group B (n=100)	Group C (n=100)	Group D (n=100)	p
Age median (min-max)	41 (26–66)	40 (21–65)	42 (24–66)	38 (22–65)	0.051
Sex (males/females)	53/47	59/41	52/48	60/40	0.556
Smokers, (n, %)	25	41	41	43	0.085
Screen Failure					
Adverse event*	-	3	4	1	0.214
Lost to follow-up	16	13	7	8	0.092

*Diarrhea, nausea and vomiting.

Table 2. Eradication rates of *H. pylori* treatment

Eradication rates	Group A (n=100)	Group B (n=100)	P	Group C (n=100)	Group D (n=100)	p
Intention-to-treat (ITT), %	63	60	0.663	72	76	0.519
Per-protocol (PP), %	75	71.4	0.728	80.9	83.5	0.792

H. pylori: Helicobacter pylori

H. pylori eradication rates tend to fall mostly due to antibiotic resistance. Thus, it is recommended to perform susceptibility testing to antibiotics for *H. pylori*, even before prescribing a new eradication treatment (14,20,21). Kadayifci et al. (11) reported that the eradication rates of *H. pylori* with triple therapy over a 10-year period showed a decline attributable to an increase in antibiotic resistance since 2000. Pooled eradication rates from 1996 to 2005 were 79.4%, 83.7%, 81.8%, 81.8%, 75.1%, 61.3%, 65.6%, 65.1%, 55.3%, and 61.1%, respectively. Also, they determined that the eradication rates were not changed by the choice of PPI and period of treatment. They suggested that rabeprazole and esomeprazole were not available in the Turkish market at that time. Eradication rates did not considerably differ when compared with 1- and 2-week regimens over the 15-year study protocol. However, over recent years, the 14-day treatment protocol achieved more excellent *H. pylori* eradication rates than just the 1-week protocol (11). Sasaki et al. (9) retrospectively searched for the correlation between *H. pylori* CAM primary resistance and eradication ratio among patients treated with the standard triple therapy as the initial step in eradication between January 1997 and December 2008. The study period was divided into 4 terms. In their study, it was found that the resistance to CAM notably increased with time from 8.7% to 34.5%, while the eradication rate considerably decreased from 90.6% to 74.8%. Thus, they revealed that the increase in primary CAM resistance is supposed as the most important point leading the decline of the initial step eradication rate based on the standard triple therapy. Gao et al. (22) documented an increase in the prevalence of CAM resistance from 12.8% to 23.8% between 2000 and 2009 in China. Similarly, the global incidence of CAM resistance in *H. pylori* is on the rise worldwide (23). Furthermore, *H. pylori* resistance to other antibiotics, such as 5-nitroimidazoles, tetracyclines, fluoroquinolones, rifamycins and nitrofurans, has been well defined (20).

This is the reason why the poor eradication rate of *H. pylori* mainly depends on antibiotic failure and patient's inaccordancy. For improving the eradication rate of *H. pylori*, alternative therapy options combined with plant extracts, probiotics, bovine lactoferrin, curcumin, honey, and antioxidants have been investigated (24-26). In the area colonized by *H. pylori*, the bacterium creates a microenvironment to induce optimal conditions for its colonization and growth. Moreover, *H. pylori* leads to the concentration of reactive oxygen intermediates (ROIs), inflammation, and the activation of immune cells (27,28). The mixed toxicity of ROIs and vacuolating cytotoxin A leads to mucosal destruction and slows down mucosal repair (27,29). The expected response of host cells against chronic oxidative stress by increasing the activities of antioxidant enzymes during *H. pylori* infection is hampered by *H. pylori*-infected cells (30). At this point, antioxidants are thought to be used as possible effective agents for *H. pylori* treatment.

Many clinical studies have demonstrated that low vitamin C levels in gastric juices and serum is correlated with a high

H. pylori rate (19,31,32). Vitamin C can inactivate the urease enzyme, which allows the endurance of *H. pylori* and the colonization of the gastric mucosa at a low pH (33). Thus, vitamin C may inhibit the spread, growth, and colonization of *H. pylori* in the early periods of infection (33). In the chronic infection period, because of a relative amount of patients occur achlorhydria leading to a higher pH of gastric juice, vitamin C may be less effective as a prophylactic agent (34). Furthermore, vitamin C affects immune cells such as neutrophils, lymphocytes, and phagocytes that play a role in oxidative activity (35,36). Vitamin E is another antioxidant that may help prevent damage to body cells by impairing the peroxidation pathway (37). Vitamin E along with vitamin C may offer some protection to people with *H. pylori* infection. Sezikli et al. (15) performed a clinical study including 160 patients taking a quadruple therapy based on PPI, AMPC, CAM, and bismuth subcitrate for 2 weeks for the treatment of *H. pylori*. The patients were divided into two groups, and one of the groups additionally received vitamin E (200 U) and vitamin C (500 mg) for 1 month. They enrolled patients with *H. pylori*-positive non-ulcer dyspepsia and low total antioxidant capacity (TAC). TAC was lower than the normal range in patients. TAC of the organism is expected to be lower in case the antioxidant mechanism is defective. The antioxidant system reflects the resistance of the organism against diseases. Supplementation with vitamins E and C in triple therapy enhanced the *H. pylori* eradication rate in patients with low TAC. In our study, we did not detect a significant difference between the groups in terms of eradication rates. However, we did not evaluate TAC of the body at the beginning of the treatment. Some patients in the present study may have normal or high TAC. Therefore, supplementation with vitamin E and C could not be effective in the eradication rate. In another study, the addition of vitamins E and C to triple therapy for 30 days was found to be significantly effective in eradicating *H. pylori* in patients with low TAC (38). Chuang et al. (39) found no additional eradication effect of vitamin E (200 U/day) and vitamin C (250 mg/day) to support triple therapy with amoxicillin, metronidazole, and lansoprazole. Kaboli et al. (40) also did not find any improvement in eradication rates using the supplementation of vitamin C in patients taking the standard triple therapy, and similar results were detected by adding vitamin C to the standard triple therapy. This strategy was found to be ineffective in another study by Koçkar et al. (41) in approximately 210 patients with *H. pylori*. Sun et al. (18) revealed that vitamin E or C supplementation brings about a few temporary preservative effects on *H. pylori*-induced gastritis in Mongolian gerbils, yet vitamin C and E supplementation did not have any beneficial impacts on *H. pylori* colonization in their study. However, there is no proof stating that the addition of vitamin C along with the standard triple therapy could be useful for eradicating the resistant infection of *H. pylori* (33,42).

In our study, we evaluated the effects of the supplementation of prescribed doses of vitamins E and C for 30 days to both triple (based on PPI, AMPC, and CAM) and quadruple (based on PPI, AMPC, CAM, and bismuth subcitrate) therapies for at least 14 days in patients with *H. pylori*. Although we did not analyses our study group with regard to Cag A positivity, antibiotic resistance, and/or TAC status, it seemed that adding vitamins E and C to the triple or quadruple therapy for the eradication *of H. pylori* was not statistically more effective. Despite some studies reporting the beneficial effects of vitamin C and E supplementation, our study indicates that this supplementation is not necessary for all *H. pylori* positive cases.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Institutional Review Board of Gülhane Military Medical Academy Hospital (18.05.2015; 1511-2913).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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