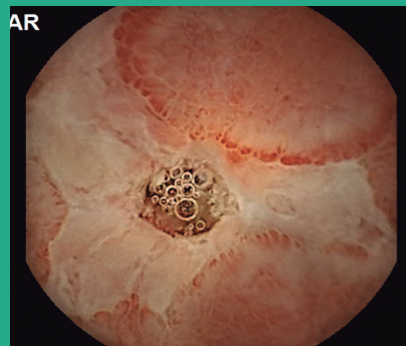
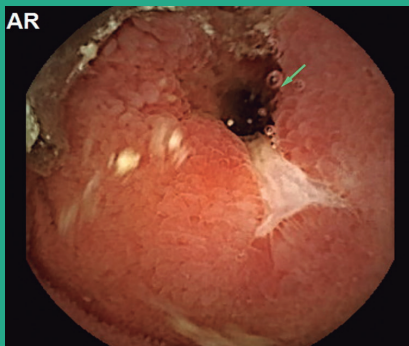


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Effectiveness of vitamins C and E adjuvant to standard triple therapy for *Helicobacter pylori* in a cohort from the Peruvian Amazon

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Abstract

Introduction and Objectives: Adjuvant therapy with vitamins C and E has been proposed to increase standard triple therapy's *Helicobacter pylori* eradication rate. This study tested this hypothesis in a cohort of patients from the Peruvian Amazon. **Material and Methods:** We retrospectively evaluated a cohort of 50 patients at Tarapoto Hospital who were treated for *H. pylori* infections from July to December 2016. Of these, 25 were randomly selected to receive standard triple therapy of 1 g amoxicillin, 500mg clarithromycin and 20mg omeprazole twice a day for 14 days plus adjuvant vitamins C and E. The other 25 only received standard triple therapy. The effectiveness of both treatments was estimated and compared using a general linear regression model using the Poisson family of distributions and log link with *H. pylori* eradication confirmed by histopathology as the outcome of interest. **Results:** A comparison of the two groups found no significant differences in their baseline symptoms, histopathological diagnoses, ages (38 ± 11 years vs. 36 ± 10 years) or genders (65% male vs. 63% male). A comparison of the effectiveness both treatments found a non-significant increase in eradication rates of 9.5% (91% vs. 82%, incidence rate ratio = 1.11; 95% confidence interval: 0.92 to 1.36). **Conclusions:** Adjuvant therapy with vitamins C and E may help increase the effectiveness of standard triple therapy for *H. pylori* in patients in the Peruvian Amazon, although this hypothesis needs to be confirmed in a clinical trial.

Keywords

Ascorbic acid; Vitamin E; drug therapy; *Helicobacter pylori*; Peru (source: Decs BIREME).

INTRODUCTION

Worldwide, *H. pylori* infections are some of the most common bacterial infections in adults. (1) In developing countries, prevalence is estimated to be above 70%, while in developed countries it is close to 35%. (2) This bacterium colonizes the stomach and usually produces symptoms in 32% of cases. The most frequent are abdominal pain, regurgitation, heartburn, nausea and hyporexia. (3) Currently, the World Health Organization (WHO) lists *H. pylori* as a type 1 carcinogen due to its close relationship with gastric cancer. (4) For this reason, and because it is a highly pathogenic microorganism, initiation of eradication therapy is recommended at the time of diagnosis. (5)

Currently, first-line *H. pylori* eradication treatment is standard triple therapy (STT) which consists of administration of two antibiotics, 2 g of amoxicillin twice daily and 500 mg of clarithromycin twice daily, and 20 mg of omeprazole, a proton pump inhibitor, twice daily for two weeks. (5) Until the last decade, the best *H. pylori* eradication rates achieved were in the range of 77% to 82%. (6, 7) Since then, various modifications have been proposed for increasing these rates. Among them are quadruple therapy, sequential therapy, hybrid therapy and adjuvant therapy with vitamins C and E. (8)

Adjuvant therapy with vitamins C and E has generated great expectations because it is relatively safe and accessible and because some reports have indicated that it can raise era-

dication rates to above 90%. (9) Vitamin C's adjuvant effect has been shown to be due to its ability to inhibit the formation of N-nitrous compounds and reactive oxygen metabolites in the gastric mucosa. (10) Both of these are considered vital for growth and carcinogenicity of *H. pylori*. (11) The adjuvant effect of vitamin E is due to its ability to inhibit lipid peroxidation and oxidative stress in the microenvironment created by *H. pylori* in the gastric mucosa. (12) These two factors are also considered to be essential factors for growth and pathogenesis of *H. pylori*. (13)

The first studies that evaluated the effects of adjuvant therapy with vitamins C and E yielded unfavorable results, (14) and the first metaanalysis published by Li in 2011 stated that there were insufficient significant findings evidence to recommend the therapy (relative risk = 0.93; 95% confidence interval (CI): 0.56 to 1.53) (15) However, newer studies show satisfactory and significant results with eradication rates for adjuvant therapy with vitamins C and E exceed those of standard triple therapy by 20%. (16) According to the latest published reports, the difference could be even larger for patients with low levels of antioxidant capacity and iron deficiency anemia. (17,18) This is very important for Peru where the prevalence of iron deficiency anemia exceeds 40%. (19) In the Peruvian jungle regions including the department of San Martín, prevalence of iron deficiency anemia is around 24%. (20) In most cases, this pathology is associated with malabsorption of iron related to low concentrations of vitamin C. (21) For this reason, our study attempts to determine the efficacy of the use of vitamins C and E, two antioxidants, as treatment adjuvant to STT for *H. pylori* in a cohort of patients from the Peruvian Amazon.

MATERIALS AND METHODS

Study Design

A retrospective cohort study was conducted in the district of Tarapoto in the province of San Martín (6 ° 29'00 " S, 76 ° 22'00 " W, population ~ 118,000) in the department of San Martín, in the northeastern region of Peru. The entire cohort consisted of patients with *H. pylori* infections diagnosed at the Social Security Hospital (EsSalud) of Tarapoto between July and December 2016. Patients who received STT plus adjuvant treatment with vitamins C and E were labeled the "exposed" cohort in this study. In order to estimate the effects attributable to adjuvant treatment with vitamins C and E, the exposed cohort was compared with a control cohort that was labelled "unexposed". For this, a random sample (1:1) was taken from hospital records by simple random sampling from the total number of patients who were diagnosed with *H. pylori* infections

and treated with STT during the same period of time. The control cohort was not exposed to adjuvant therapy with vitamins C and E. To compare the effectiveness of the treatment, both cohorts (exposed and unexposed) were followed retrospectively to measure and compare the eradication rates of *H. pylori*. In order to avoid information bias, eradication of *H. pylori* was defined a priori as a confirmed histopathological and upper endoscopy diagnosis.

Population and Sample

The exposed cohort and the unexposed cohort consisted of patients who were adults aged 18 to 60 years old, who had symptoms of abdominal pain, regurgitation, heartburn, nausea and/or hyporexia, and who had been diagnosed histopathologically with *H. pylori*. The exposed cohort consisted of those patients treated during the study period while the unexposed cohort was chosen randomly (sample 1: 1) from among all patients who had been diagnosed and treated previously and who met the criteria. Both cohorts received STT, but only the exposed cohort also received adjuvant treatment with vitamins C and E. Patients were excluded if they had had prior treatment for *H. pylori*, histories of gastric or duodenal ulcers, neoplasms of any kind, had been diagnosed as carriers of any metabolic disease, if they were pregnant or lactating women, if they had been treated with antibiotics in the six months prior to the study, if they were allergic to penicillins or other antibiotics, and if they had histories of previous gastric surgery. The sample size was estimated on the basis that a minimum of 50 patients (25 exposed and 25 unexposed) would be required to find differences in eradication rates over 25%, a 70% eradication rate was assumed in the unexposed, and an exploratory 90% CI and a study power of 80% were set. To maximize the power of study, from the beginning we planned to include all patients who met the selection criteria during the study period

Standard Triple Therapy for *H. pylori*

STT was provided for free to all patients by the Social Security hospital (EsSalud) of Tarapoto. STT, considered the first line *H. pylori* treatment, (8) consists of twice daily oral administration of 1 g of amoxicillin, 500 mg of clarithromycin, and 20 mg of omeprazole for 14 days.

Standard Triple Therapy Plus Adjuvant Treatment with Vitamins C and E

The use of STT plus adjuvant treatment with vitamins C and E is a potential new alternative therapy for *H. pylori*. It consists of twice daily administration of 500 mg of vitamin

C and 200 IU of vitamin E until 30 days after the completion of STT. (9)

Data Collection

The medical records from the Social Security hospital (EsSalud) in Tarapoto of all of these patients were used as the primary source of information. In the case of the exposed cohort, all data of interest were identified by the principal investigator (Wildor Samir Cubas, WSC) and taken from patients' medical records. For the unexposed patients, a form was first elaborated with patients' medical record numbers in chronological order. Next, the sample was taken, and then the data was collected. In both cases, age, gender, work environment, origin, main symptoms, disease duration and endoscopic and histopathological findings before and after therapy were recorded. All the variables of interest were measured in the standard way and collected retrospectively from the medical records of each study subject. To facilitate data collection, a checklist with ranges of values and pre-established categories was developed to ensure reliable data collection. Once this process was finished, the data were typed in duplicate and any discrepancies were resolved by another review of the medical records.

Data Analysis

Our descriptive analysis of baseline clinical-epidemiological characteristics of the study population included standard deviations (SD) of quantitative variables and absolute and relative frequencies of qualitative variables. Fisher's exact test and the χ^2 test were used for comparison of proportions of the baseline characteristics of the exposed and unexposed. A multivariate Poisson regression analysis was performed to estimate the efficacy attributable to adjuvant therapy with vitamins C and E. The nested model method controlled by baseline characteristics was used to isolate the effect of adjuvant treatment. In this analysis, age, gender, adherence to treatment, disease time and number of symptoms were taken as potential confounding factors. In all cases, data analysis was performed using the STATA MP v13 statistical package considering a 95% CI.

Ethical Considerations

The ethics committee of the Hospital Nacional Docente Madre Niño "San Bartolomé" in Lima, Peru reviewed and approved the protocol of this study. The confidentiality of information was respected although informed consent was not necessary because the data was obtained retrospectively.

RESULTS

Study Population Characteristics

Between July and December 2016, a total of 50 patients with *H. pylori* infections were evaluated and received eradication therapy. Of these, five patients (10%) were excluded from the analysis because they did not complete treatment. Of these five, two belonged to the exposed group and three belonged to the unexposed group. Among the 45 patients analyzed, no differences were found between exposed and unexposed patients (23 versus 22) in terms of male predominance (65% vs. 64%) and average age (38 ± 11 versus 36 ± 10 years), which was 37 ± 11 years (range: 19-59 years). The majority of patients came from the city of Tarapoto (74% versus 64%), and the rest came from rural areas of the town's periphery (26% versus 36%). The majority worked in the public sector (52% vs. 63%), and the rest were private sector workers (39% vs. 31%) or unemployed (9% vs. 5%). The main reason these patients came to the Gastroenterology Department of the Social Security Hospital (EsSalud) in Tarapoto was abdominal pain (43% versus 40%) which was followed by regurgitation (22% versus 27%), heartburn (17% vs. 18%), hyporexia (13% vs. 5%) and nausea (4% vs. 9%). Clinical manifestations had presented more than seven days prior to coming to the hospital in most cases (74% versus 77%). According to endoscopic findings prior to eradication therapy, the most frequent gastric lesions were antral gastritis (43% vs. 55%), pangastritis (43% vs. 27%) and mild intestinal metaplasia (13% versus 18%).

Efficacy of *H. Pylori* Eradication Therapies

The overall efficacy of *H. pylori* eradication therapies, the eradication rate, was estimated at 87% (95% CI: 76% to 97%). That for the exposed group was 91% (95% CI: 79-100%) while that for the unexposed group was 82% (95% CI: 64-99%). Based on these eradication rates, a ratio of incidence rates of 1.12 (95% CI 0.88 to 1.41) was calculated.

DISCUSSION

Adjuvant therapy with vitamins C and E has been reported to be an effective alternative for increasing the eradication rate of *H. pylori* attributable to STT. Although this may be the case for *H. pylori* patients in the Peruvian Amazon, the results of our study do not allow us to make this conclusion even though our data indicate that adjuvant therapy increased the eradication rate by 9.5% (91% vs. 82%; incidence rate ratio = 1.11; 95% CI: 0.92 to 1.36). Nevertheless, this effect was statistically not significant (Figure 1). This could

be because the effect does not exist or because it exists, but its magnitude is too small to have been detected with a power of study as small as ours.

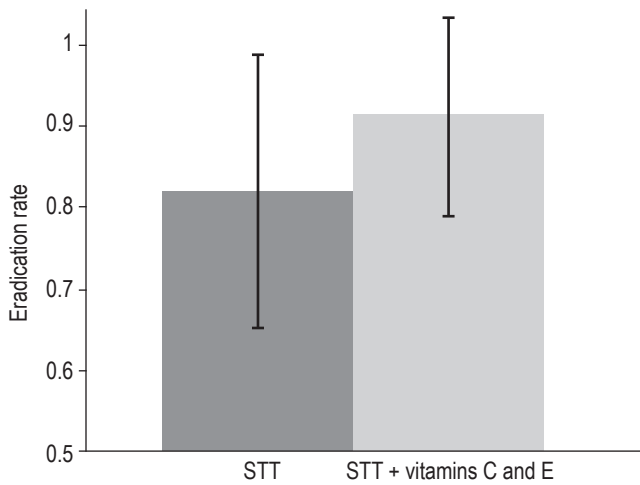


Figure 1. Effectiveness attributable to adjuvant use of vitamins C and E with standard triple therapy for patients infected with *H. pylori* in the Peruvian Amazon. Adjuvant treatment with vitamins C and E may increase eradication rates obtained with STT in patients infected with *H. pylori* (91% vs. 82%, incidence rate ratio = 1.11; 95% CI : 0.92 to 1.36).

According to several previous studies, the eradication rates attributable to STT plus adjuvant vitamins C and E can be as high as 94%. (9) This eradication rate is very similar to the 91% found in our study (Table 1). These rates may be explained by deficiencies of its antioxidant capacities of the populations studied. This was evidenced in an experimental study carried out in Asia where the patients in the sample infected with *H. pylori* also had low levels of antioxidant capacity. After administration of eradication therapy plus adjuvant vitamins C and E, eradication rates were higher than with standard triple therapy. (16) Subsequent studies have found that low levels of antioxidants are related to increased virulence and persistence of *H. pylori*, and that increasing antioxidant levels can affect survival of the bacteria. (22, 23) Another factor involved in *H. pylori* pathogenesis is its direct relationship with iron deficiency anemia in infected individuals resulting from poor absorption of iron when concentrations of antioxidants are low. This is the case with vitamin C in patients with *H. pylori* infections. (17, 21) This may add to the problem in South American countries like Peru where the latest reports of *H. pylori* prevalence and anemia exceed 60% and 40%, respectively. (19, 24). In the Peruvian Amazon, including the department of San Martín, anemia's prevalence is approximately 24%. (20)

Table 1. Eradication rate of *H. Pylori* according to exposure to therapy with vitamin C and E

Variables	Exposed		Not exposed	
	n	%	n	%
Eradication				
Yes	21	91	18	82
No	2	9	4	18
Total	23	100	22	100

Source: clinical records of patients infected with *H. pylori* from the Gastroenterology Service of the Social Security Hospital (EsSalud) of Tarapoto between July and December 2016.

The findings of our work indicate that STT plus adjuvant vitamins C and E has therapeutic results that are superior to those of STT alone (91% vs. 82%). Given the close relationship between *H. pylori* infections, anemia, and low levels of antioxidants, we can infer that supplementing eradication therapies with vitamins C and E may have indirectly improved antioxidant levels in this study's subjects which could have contributed to raising the *H. pylori* eradication rate above that of STT alone. Although some studies done in the past decade suggest that the evidence for recommending this adjuvant therapy is insufficient, (15) a number of other studies have demonstrated its therapeutic effectiveness. (25-27)

As in other studies, *H. pylori* infections were observed most frequently in male adult patients (24, 28, 29, 30, 31) However, contrary to expectations, the majority of patients infected with *H. pylori* (68%) came from urban areas of Tarapoto while a minority came from rural areas (Table 2). This may be due to a design effect, since *H. pylori* infections are commonly reported to be associated with poor socioeconomic conditions and poor basic services with limited access to drinking water. However, in Peru potable water does not seem to prevent new *H. pylori* infections. In fact, according to a recent study carried out in Lima, where the majority of the population has access to drinking water, it is common to find remains of *H. pylori* genetic material in drinking water. (32) What is even more worrisome is that strains of *H. pylori* that are resistant to standard levels of sodium hypochlorite (chlorine) are not uncommon, either. (33)

In conclusion, adjuvant treatment with vitamins C and E may increase the effectiveness of standard triple therapy for *H. pylori* in patients in the Peruvian Amazon. Nevertheless, to demonstrate this conclusively more experimental research is needed.

Table 2. Population characteristics

Variables	Exposed		Unexposed	
	n	%	n	%
Sex				
Male	15	65 %	14	64 %
Female	8	35 %	8	36 %
Place of residence				
Tarapoto	17	74 %	14	64 %
Periphery	6	26 %	8	36 %
Labor sphere				
Public	12	52 %	14	63 %
Private	9	39 %	7	32 %
Unemployed	2	9 %	1	5 %
Reason for consultation				
Abdominal pain	10	43 %	9	41 %
Regurgitation	5	22 %	6	27 %
Heartburn	4	17 %	4	18 %
Hyporexia	3	13 %	1	5 %
Nausea	1	4 %	2	9 %
Disease duration				
> 7 days	17	74 %	17	77 %
< 7 days	6	26 %	5	23 %
Initial histopathology				
Antral Gastritis	10	43 %	12	55 %
Pangastritis	10	43 %	6	27 %
Intestinal metaplasia	3	14 %	4	18 %

Source: clinical records of patients infected with *H. pylori* from the Gastroenterology Service of the Social Security Hospital (EsSalud) of Tarapoto between July and December 2016.

Authorship Contributions

WSC, RRC, HAR and AMQ participated in the design of the study, the interpretation of the results and the writing of the manuscript. In addition, WSC, RRC and HAR participated in data collection; and AMQ participated in data analysis.

Conflicts of Interest

The authors declare that they have no conflicts of interest related to this article.

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