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Alimentary Tract

Ten-day empirical sequential or concomitant therapy is more effective than triple therapy for *Helicobacter pylori* eradication: A multicenter, prospective study

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ABSTRACT

Background: The resistance of *Helicobacter pylori* to antibiotics has increased the need for new empirical, first-line treatments. However, the efficacy of sequential therapy (ST) and concomitant therapy (CT) compared with triple therapy (TT) has not been adequately evaluated.
Aim: In this study, we evaluated the efficacy of these empirical three regimens.
Methods: The 517 patients enrolled in the study were prospectively randomized to receive 10 days of TT ($n = 171$), ST ($n = 170$), and CT ($n = 176$) at 5 university-affiliated hospitals from May 2013 to March 2015. The post-treatment *H. pylori* status was determined using the ^{13}C-urea breath test.
Results: The baseline characteristics were similar among the three groups. The intention-to-treat eradication rates were 62.6%, 70.6%, and 77.8% in the TT, ST, and CT groups, respectively ($p < 0.01$). The corresponding per-protocol eradication rates were 82.8%, 89.5%, and 94.4%, respectively ($p < 0.01$). There were no significant differences in the compliance, side effects, and follow-up loss rates.
Conclusion: A higher eradication rate was achieved with empirical 10-day ST, and CT than with the TT regimen, with similar rates of compliance and treatment side effects.

1. Introduction

Helicobacter pylori is a gram-negative bacillus that causes chronic gastritis, peptic ulcer disease (PUD), mucosa-associated lymphoid tissue lymphoma, and gastric cancer [1]. Recent global consensus recommends that all *H. pylori*-positive individuals receive eradication therapy to prevent both the recurrence of PUD and the development of gastric cancer. In addition, because *H. pylori* is an infectious agent, other individuals are at risk [2]. The current first-line treatment choice for *H. pylori* eradication is triple therapy (TT), consisting of a proton pump inhibitor (PPI), clarithromycin, and amoxicillin, for 7–14 days [3,4]. During the past few decades, TT has become less effective, such that the eradication rates in some countries, including Korea, are around 80% [5,6]. The lower eradication rates are due primarily to the increased resistance of *H. pylori* to several major antibiotics, including clarithromycin, metronidazole, and fluoroquinolone, indicating the need for new empirical first-line treatments.

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Among the most promising of the new therapeutic strategies are the non-bismuth four-drug therapies [7]. These sequential and concomitant regimens add metronidazole to TT for different durations and in different combinations. Specifically, sequential regimens consist of a two-stage protocol, in which amoxicillin and a PPI are administered during the first stage. Together, these two agents weaken the bacterial cell wall, thus maximizing the effect of the second-stage antibiotics (metronidazole and clarithromycin). While initially promising, however, this approach seems to be less effective in populations with high metronidazole resistance, as in Korea [8]. In concomitant therapy (CT), the patient is first treated with TT plus metronidazole in an attempt to overcome the clarithromycin and metronidazole resistance of the bacterium. Several studies have compared TT vs. ST, TT vs. CT [9], and ST vs. CT [10] in the Korean population, but there are few reports in which these three regimens were compared directly. Therefore, in this multicenter, prospective study, we compared the eradication rates of 10-day TT, ST, and CT in a cohort of consecutive Korean patients from an area with higher antibiotic resistance. We also evaluated treatment compliance and the side effects associated with treatment.

2. Materials and methods

2.1. Patients and study design

This multicenter, prospective, randomized, open-label study was conducted from May 2013 to March 2015. Treatment-naïve patients with *H. pylori* infection were enrolled at five university-affiliated centres in the cities of Bucheon (Western Kyonggi) and Incheon, South Korea. Each patient underwent esophagogastroduodenoscopy, during which at least two antral and two corpus biopsies were taken for the detection of *H. pylori*. Positivity for Giemsa staining was regarded as positivity for *H. pylori*. The indications for *H. pylori* eradication were PUD, mucosa-associated lymphoid tissue lymphoma, and early gastric cancer after endoscopic submucosal dissection, as strongly recommended by the guidelines of the Korean Society for Gastroenterology [4]. For the PUD patients, PPI was given before the eradication regimen. However, PPI was discontinued at the least two weeks before starting eradication regimen.

The exclusion criteria were as follows: (1) treatment with antibiotics, bismuth, or non-steroidal anti-inflammatory drugs during the previous 4 weeks; (b) a history of gastric surgery; (c) severe systemic illness, such as liver cirrhosis or kidney failure; (d) allergy to any of the antibiotics used in the study; (e) pregnancy; and (f) age of <18 years. Each included patient provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of each participating hospital. The study is registered at the Clinical Research Information Service (KCT0000703) and was approved by the Ministry of Food and Drug Safety.

Treatment compliance was evaluated by a physician and was based on each patient's diary as well as pill counting. A patient was considered noncompliant if he/she took <90% of the study medications. Patients were asked to record any adverse effects in their diaries.

2.2. Randomization and intervention

A computer-generated randomization system was used to randomize the patients in a 1:1:1 manner to receive one of three regimens: (a) TT (40 mg of pantoprazole, 500 mg of clarithromycin, and 1000 mg of amoxicillin twice daily) for 10 days, (b) ST (40 mg of pantoprazole and 1000 mg of amoxicillin twice daily for 5 days, followed by 40 mg of pantoprazole, 500 mg of metronidazole, and 500 mg of clarithromycin twice daily for the remaining 5 days), or (c) CT (40 mg of pantoprazole, 1000 mg of amoxicillin, 500 mg of metronidazole, and 500 mg of clarithromycin twice daily for 10 days).

2.3. [^{13}C]-urea breath test

H. pylori eradication was defined as a negative [^{13}C]-urea breath test (UBT) performed at least 4 weeks after treatment completion. During treatment, no patient was allowed a PPI, bismuth, an H2 blocker, or antibiotics. All breath samples were collected and analyzed at the individual centres. The patients fasted for 4 h before testing, and a pre-dose breath sample was obtained in the absence of a pre-test meal. Each patient was orally administered 100 mg [^{13}C]-urea (UBiTkit®; Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan), and a second breath sample was collected 20 min later. The cut-off value was 2.5‰. Breath samples were analyzed using an isotope-selective, non-dispersive infrared spectrometer (UBiT-R 300; Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan).

2.4. Statistical analysis

2.4.1. Sample size calculation

We calculated the sample size needed to detect a difference of 13% in the eradication rates between the four-drug therapy groups (ST and CT: assuming an eradication rate of 85%) and the TT group (assuming an eradication rate of 72%), with a power of 80% and a significance level of 0.05 ($\alpha = 0.05$, two-sided). A dropout rate of 10% was anticipated. The final calculated sample size was 510 patients (at least 170 patients per group).

2.4.2. H. pylori *eradication rate*

Intention-to-treat (ITT) and per-protocol (PP) analyses were performed to compare the *H. pylori* eradication rates between groups. Because of the unexpectedly high follow-up loss rate (20%), we used a sensitivity analysis, which calculated the ITT (either bad, in which all cases of follow-up loss were regarded as UBT-positive, or good, in which all cases of follow-up loss were regarded as UBT-negative), the FW (four-drug group worst, in which cases of follow-up loss in the TT/ST and CT groups were regarded as UBT-negative/positive), TW (triple therapy worst, in which cases of follow-up loss in the TT/ST and CT groups were regarded as UBT-positive/negative), and the overall ITT eradication rate (in which cases of follow-up loss in each arm were regarded as UBT-positive according to the positive rate of each arm). Categorical variables are reported as numbers and percentages and were compared using the χ^2 test. Continuous variables are reported as the mean ± standard deviation and were compared using one-way analysis of variance. The upper and lower limits of the 95% confidence intervals (CIs) of the eradication rates were also determined. All statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered to indicate statistical significance.

3. Results

3.1. Patients

The mean age of the 517 patients included in this study was 52.7 ± 12.4 years, and 67.5% were male. The demographic characteristics of the ITT populations were similar among the three groups (Table 1). Fig. 1 is a schematic diagram of the study. Of the 171 patients in the TT group, 43 dropped out (37 were lost to follow-up, and 6 discontinued therapy due to poor compliance). Of the 170 patients in the ST group, 37 dropped out (36 were lost to follow-up,