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First-line treatment of *Helicobacter pylori* in Lebanon: Comparison of bismuth-containing quadruple therapy versus 14-days sequential therapy

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ABSTRACT

Helicobacter Pylori (*H. Pylori*) is the most common cause of peptic ulcer disease (PUD) and represents a strong risk factor for gastric cancer. Treatment of *H. Pylori* is, *therefore*, a persistent need to avoid serious medical complications. Resistance to antibiotics remains to be the major challenge for *H. Pylori* eradication. In this study, we determined the prevalence of *H. pylori* infection and evaluated *H. pylori* eradication efficacy of bismuth-containing quadruple therapy (Pylera) versus 14-days sequential therapy in treatment naïve-Lebanese patients. 1030 patients, showing symptoms of peptic ulcer (PU) and gastritis, underwent ^{14}C-Urea Breath Test and esophagogastroduodenoscopy to examine *H. Pylori* infection and gastrointestinal disorders. Among the *H. Pylori*-positive patients 60 individuals were randomly selected, separated into two groups (each consisting of 30 patients) and treated with either bismuth-containing quadruple therapy or 14-days sequential therapy. We show that of the 1050 patients tested: 46.2% were *H. pylori*-positive, 55% had gastritis, 46.2% had both gastritis and *H. pylori* infection, 8.8% had gastritis but no *H. pylori* infection, 44.9% had neither gastritis nor *H. pylori* infection. Following the 14-days sequential therapy, the eradication rate was significantly higher than that obtained upon using bismuth-containing quadruple therapy [80% (24/30) versus 50% (15/30), $\chi^2 = 5.93$, P = 0.015]. In conclusion, we determined *H. pylori* and gastritis prevalence among Lebanese PU-patients and showed that 14-days sequential therapy is more efficient than bismuth-containing quadruple therapy in terms of *H. Pylori*-eradication.

1. Introduction

Helicobacter Pylori (*H. Pylori*) is a spiral-shaped gram-negative bacteria capable of producing the urease enzyme enabling it to colonize the human stomach [1,2]. *H. Pylori* infection is described to be associated with serious pathologies including chronic inflammation of the stomach lining (gastritis), gastric and duodenal ulcer, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma [3]. Individuals infected can be asymptomatic or show occasional episodes of abdominal discomfort, bloating, belching, nausea and vomiting. *H. Pylori* is considered as one of the most worldwide prevalent chronic infections with about more than 50% of the world's population being infected [4]. Remarkably, the incidence, prevalence and age distribution of *H. Pylori* infection greatly differs between developing and developed countries [4]. For instance, and despite the fact that it is diminishing in both developing and developed, the prevalence of *H. Pylori* infection is higher in developing than developed countries [4]. This is mostly associated with the low socioeconomic status and poor hygienic conditions in developing areas. Different modes of *H. Pylori* infection transmission has been indicated among which are oral-oral, fecal-oral and gastric-oral routes [4,5]. Diagnosis of *H. Pylori* infection can be achieved by invasive techniques involving endoscopy and biopsy (such as direct microscopic examination, rapid urease test, culture and molecular evaluation of biopsy samples) and by non-invasive approaches, including the ^{13}C- or ^{14}C-urea breath test, ^{13}C-urea blood test and fecal antigen test [6]. People with active gastric or duodenal ulcer

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should be examined for *H. pylori* infection and need to be efficiently treated if found to be infected. Eradication of *H. pylori* can facilitate ulcer healing, minimize ulcer complications (like bleeding) and reduces the risk of having new ulcers. As no single drug is yet able to cure *H. pylori* infection, currently, most treatment regimens include a 7–14 days mixed therapy consisting of one or two effective antibiotics (such as amoxicillin, clarithromycin, metronidazole and tetracycline) plus either a bismuth (a heavy metal with antimicrobial activity) or a proton pump inhibitor (PPI; such as esomeprazole, lansoprazole, omeprazole) that suppress stomach acidity [7,8]. However, bacteria-resistance to antibiotics remains a major challenge for achieving a successful *H. pylori* therapy [9–11]. In this study, we aimed at determining the prevalence of *H. pylori* infection and comparing the efficacy of bismuth-containing quadruple therapy (Pylera) versus 14-days sequential therapy as a first line-treatment against *H. pylori* in Lebanese PU-patients.

2. Materials and methods

2.1. Study design

This work corresponds to a prospective, randomized, open-label, controlled study, performed at Raee hospital between January 2015 to August 2016, analyzing 1030 treatment-naïve patients [600 females (58.25%) and 430 (41.75%) males] with abdominal pain and symptoms of PU and gastritis. Esophagogastroduodenoscopy was applied for all patients, during which at least two antral and two corpus biopsies were obtained. All of the patients were tested for *H. pylori* infection. Positivity for infection was considered after achieving positive results for both assays: (1) Giemsa staining of the endoscopic biopsies and (2) PY test (^{14}C-Urea Breath Test); During this study, patients were excluded if they had any of the following criteria: (1) were younger than 18 years or older than 80 years; (2) were pregnant; (3) had used bismuth, antibiotics or non-steroidal anti-inflammatory drugs during the past 4 weeks prior to the test; (4) had been subjected to gastric surgery; (5) had a severe medical illness such as liver or kidney failure; or (6) showed allergic reactions to any of the drugs used. This work was conducted in accordance with the Declaration of Helsinki (1964) and after obtaining approval of the local patient safety and risk management committe of the “Raee hospital” (Lebanon). Informed consent was obtained from all patients included in this study.

2.2. PY test (^{14}C-Urea breath test)

This test was performed using PYtest® Kit (TRI-MED) following the manufacturer's instructions. All breath samples were collected and analyzed at Raee Hospital. Patients were not allowed to take antibiotics- and bismuth-containing drugs for 1 month, PIPs for 1 week and cyto-protective medicines for 2 weeks prior to the test. Patients fasted for 4 h prior to the test and a predose breath sample was obtained. Each patient was given, orally, a PYtest® capsule (containing a small amount of ^{14}C-labelled urea). Ten minutes later, a breath sample was collected in a special metalised mylar balloon. The quantity of radioactive carbon-dioxide ($^{14}CO_2$) was then determined using microCOUNT Lite machine. Following the manufacturer's guidelines, a positive test was considered when $^{14}CO_2$ excretion > 200 dpm, a negative test when < 50 dpm and a border line positive test when 50 dpm > $^{14}CO_2$ excretion < 200 dpm. Respecting the manufacturer's recommendations, whenever a borderline Positive was obtained the same breath sample was re-counted again in the microCOUNT Lite machine after 20 min.

2.3. Randomization and intervention

60 patients (30 males and 30 females), with *H. pylori*-positive gastritis, were included for the purpose of treatment. Randomization was carried out in blocks of 15. All randomization codes were deposited in sealed opaque envelopes and kept by an independent researcher. After obtaining informed consent, the researcher was asked to open the envelope for the allocated regimen. 30 patients (15 males and 15 females; group 1) were treated with Pylera® (three-in-one capsules containing bismuth subcitrate potassium 140 mg, metronidazole 125 mg, and tetracycline 125 mg) 3 capsules four times a day plus ezomeprazole 40 mg two times a day for 10 days, whilst group 2 patients received sequential therapy (ezomeprazole 40 mg and amoxicillin 1000 mg twice daily for 7 days, followed by ezomeprazole 20 mg, metronidazole 500 mg, and clarithromycin 500 mg twice daily for the remaining 7 days). *H. pylori* eradication was considered when ^{14}C-Urea Breath Test, performed at least 4 weeks after treatment completion, was negative. During that period, patients were not allowed to have a PPI, bismuth or antibiotics.

2.4. Statistical significance

To study the relationship between the type of used therapy and efficacy rate, chi square (χ^2) test was carried out. P value < 0.05 was considered significant.

3. Results

The mean age of the 1030 patients, included in this study, was 40 ± 10. Following PY test and Esophagogastroduodenoscopy, being performed within 12–24 h, we found that 476 patients (46.2%) [182 males (17.6%) and 294 females (28.6%)] were *H. pylori*-positive (Fig. 1). Interestingly, all of the *H. pylori*-positive patients appeared to have gastritis (defined by the presence of neutrophils and/or mononuclear cells) (Fig. 1). On the other hand, only 91 members (16.4%) of the *H. pylori*-negative patients had gastritis (Fig. 1). Intriguingly, among the patients with gastritis, gastric erosions were detected in *H. pylori*-positive ones, mainly whereas the majority of the *H. pylori*-negative ones were PPI users. Altogether, these observations reveal that among the 1030 patients examined: 46.2% were *H. pylori*-positive, 53.8% were *H. pylori*-negative, 55% had gastritis, 45% had no gastritis, 46.2% had gastritis and were *H. pylori*-positive, 8.8% had gastritis and were *H. pylori*-negative, 44.9% had no gastritis and were *H. pylori*-negative, 0% had no gastritis and were *H. pylori*-positive.

Of the 476 *H. pylori*-positive patients, 60 individuals were randomly selected (30 females and 30 males) and randomly divided into two groups, each consisting of 30 patients (15 females and 15 males). Patients of the first group were treated by bismuth-containing quadruple therapy (Pylera), while members of the second group were provided with a sequential therapy (Fig. 1). *H. pylori* eradication was considered when PY Test, performed at least 4 weeks after treatment completion, showed negative results. Intriguingly, Pylera showed less eradication efficiency than sequential therapy as *H. pylori* eradication was detected in only 15 patients (50%) of group 1 (treated with Pylera) versus 24 patients (80%) in group 2 (treated with sequential therapy) (Figs. 1 and 2).

4. Discussion

Infection with *H. pylori* can cause a wide range of serious gastrointestinal complications such as peptic ulcer and gastric cancer. An accurate diagnosis and eradication of *H. pylori* in PU-infected patients is important for ulcer healing and prevention of recurrent hemorrhaging. The worldwide prevalence of *H. pylori* differs significantly between developing and developed countries where the former are characterized by much higher infection rates [12,13]. Determination of the prevalence of the infection, is therefore, important to define the extent and magnitude of its impact on the public health in a certain region. In Lebanon there is only few information about *H. pylori* infection prevalence and eradication. In fact, a previous study examined *H. pylori* infection in North Lebanon between September 1 1996 to March 31 1998 upon testing 349 patients, using the modified urease technique and biopsy tissue obtained following esophagoduodenoscopy, and