Original Article
Effect of gastric acidification on the 14C-UBT HELIPROBE® accuracy during Pantoprazole treatment in *Helicobacter pylori* positive patients

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Abstract: The aim of this study was to evaluate the influence of using Citric Acid on false negative rates induced by PPIs during 14C–UBT in dyspeptic patients with *H. pylori* infection. In a crossover randomized controlled clinical trial, one hundred dyspeptic patients (46 females and 54 males) with determined *H. pylori* infection who referred to gastrointestinal Outpatient Clinic of Razi Hospital-Rasht, Iran. All the patients underwent a 14C-UBT HELIPROBE® baseline test and the positive ones entered the second phase. They were divided randomly to two groups and started PPIs treatment by Pantoprazole (20 mg/daily Pantozol® Nycomed Company) and underwent two other UBTs in days 12-13 and 14-15 with and without 4 grams Citric Acid. In group I who underwent UBT with Citric Acid in days 12-13 (UBT$_2$) and UBT without Citric Acid in days 14-15 (UBT$_3$), there was no significant difference between the UBT results with and without Citric Acid (P≥0.05). In group II who underwent UBT without Citric Acid in days 12-13 and UBT with Citric Acid in days 14-15, the false negative rates were not significantly different between UBT with and without Citric Acid (P≥0.05). In both groups the results of UBT without Citric Acid after Pantoprazole consumption didn't change significantly compared to the baseline UBT. Also the difference between the false negative rates of baseline UBT and UBT without citric acid was not significant (P>0.05). These results suggest that acidification of gastric environment during 14C-UBT cannot prevent false negative results and do not increase the accuracy of the test in patients taking PPIs.

Keywords: Helicobacter pylori, urea breath test, citric acid

Introduction

Helicobacter pylori, spiral-shaped gram-negative organism is thought to infect the stomachs of 60% of the world's adult population [1, 2] and its infection being present in 60%–80% of gastric and 95% of duodenal ulcers [3]. There is good evidence for infection with this organism as the principle cause of acute, chronic and atrophic gastritis [4]. *H. pylori* has now been classified as a definite carcinogen by the World Health Organization, because of its epidemiologic relationship to gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma [3, 5]. People usually remain infected throughout life without specific treatment and individuals from developing countries might have a higher risk of gastric cancer because infection in these countries typically occurs in childhood [6, 7]. According to population-based studies, it has been shown that the *H. pylori* infection rate is very high in the Iranian population [8, 9].

After being ingested, Urease hydrolyzes urea into carbon dioxide and ammonia, thereby per-

mitting *H. pylori* to survive in an acidic environment. The enzyme activity is regulated by a unique pH-gated urea channel [10].

H. pylori infection can be diagnosed by noninvasive methods or by endoscopic biopsy of the gastric mucosa [10, 11]. Noninvasive methods include the urea breath test, serologic tests, and stool antigen assays [10, 12]. Urea breath testing (UBT) which relies on the abundant, *H. pylori*–derived Urease activity in the stomach, effectively detects active infection [6, 10, 13-15]. Since the original description of C-UBT by Graham et a1, several modifications have been published aiming at simplifying and optimizing the test [16, 17]. The principle of the UBT relies upon the ability of the Urease, produced by *H. pylori* to hydrolyze the "labeled carbon-containing urea" and breaks down any urea to ammonia and carbon dioxide (CO_2) in the gastric mucosa, which finally, tagged carbon within the liberated CO_2 is detected in exhaled breath samples [3, 8, 16, 18]. Two UBTs are now approved by the US-FDA, ^{13}C based test and ^{14}C based test. The both types of UBT are quite similar in sensitivity (90% to 96%) and specificity (88-98%) [13, 19, 20]. The ^{13}C isotope has the difficulty of requiring more complex equipment, such as a mass spectrophotometer. However, the required equipment for the ^{14}C isotope is only a portable compact beta-scintillation counter, which offers performing the test in the offices [8, 21]. The main advantages of the HELIPROBE ^{14}C-UBT are its rapidity and patient convenience. Furthermore, in view of the very low radioactivity of the ^{14}C-UBT and its portability, this test seems to be a more suitable option for office use than nonradioactive, complex and off-site ^{13}C-UBT as well as other invasive diagnostic modalities [8].

Despite its high validity, many factors have been reported by different surveys that cause false negative UBT including proton pump inhibitors (PPIs), H_2 receptor antagonist, bismuth, and antibiotics [13]. PPIs are highly effective in the treatment and symptomatic relief of peptic ulcer, and as part of combination therapy for *H. pylori* eradication [22]. False negative urea breath test (UBT) results have been reported to occur in up to 40% of individuals taking proton pump inhibitors [15, 23]. Although the mechanisms remain unclear, several hypotheses have been suggested to explain it. One is related to the effect of the PPIs on intragastric pH [22],

which could make the intragastric environment unattractive for *H. pylori* and thus indirectly reduce the bacterial load. Alternatively, the increased pH could be sufficient to close the postulated urea channel, and thus reduce urea's access to *H. pylori* urease [23]. For this reason, it is currently recommended cessation of PPIs 1 to 2 weeks before the UBT [22, 24]. Unfortunately, this recommendation is not practical and desirable for patients who often suffer from significant acid-mediated symptoms when their PPI is withheld [15]. Considering the hypothesis that PPIs induce false negative UBT results by a PH dependent mechanism, some surveys have recently published that suggest manipulation of intragastric PH may significantly decrease the false negative results associated with 14 days treatment of some PPIs, independent of UBT methodology [20, 22]. It has been postulated that the acidification of the stomach by co-administration of Citric Acid and urea would reverse any pH effect of PPIs and possibly prevent false negative UBT results [15]. Regarding there is little information currently available on the effect of Citric Acid on false negative UBT results (specially ^{14}C-UBT) in patients on standard doses of different proton pump inhibitors in a high prevalent region like Iran, we are evaluating the influence of using Citric Acid on false negative rates induced by PPIs during ^{14}C–UBT in dyspeptic patients in North of Iran.

Materials and methods

Subjects

One hundred dyspeptic patients (46 females and 54 males) who referred to gastrointestinal Outpatient Clinic of Razi Hospital -related to Gastrointestinal and Liver Diseases Research Center (GLDRC) of Guilan University of Medical Sciences-and their *H. pylori* infection was determined by UBT, RUT, Stool antigen or Histology were enrolled in the study from February 2011 to January 2012. Inclusion criteria consisted of age ≥ 18 years old, written consent by the participants, the diagnosis of *H. pylori* infection, and start of PPIs treatment. The subjects who had the history of previous gastric surgery, taking antibiotics 4 weeks before the first UBT or during the survey, participating in clinical study during last 30 days previous to the first (screening) visit, other significant clinical disorders which make the patient inappropriate for the

study, administration of PPIs or H_2 blockers within 4 wk before the date of entry, pregnancy, recent history of peptic ulcer or esophagitis complications, the previous *H. pylori* treatment and history of chronic liver and kidney diseases were excluded from the study.

The protocol was approved by ethical community of Gastrointestinal and Liver Diseases Research Center (GLDRC) of Guilan University of Medical Sciences which was registered under IRCT201105221155N12 at the Iranian Registry of Clinical Trials (www.irct.ir).

Study design

This study was a crossover randomized controlled clinical trial. For all the subjects who had written consent to enter the survey, standard screening UBT (UBT$_1$) was performed in the first phase and the patients with positive tests entered the second phase. In the second phase, the patients were administered PPIs for 15 days and randomly (by Random Block method) were divided to two different groups (50 individuals in each group). The administered PPI was 20 mg per day Pantoprazole (Pantozol® from Nycomed Company) 1/2 hour before breakfast.

Group I: Two other UBTs were performed in these patients. The first one (UBT$_2$) was performed after 12-13 days of taking PPIs simultaneously with the administration of 4 grams Citric Acid (modified UBT) and the second one (UBT$_3$) was performed after 14-15 days of PPIs consumption and without Citric Acid addition.

Group II: They were undertaken UBT (UBT$_2$) after 12-13 days of PPIs consumption without Citric Acid administration and in day 14-15 (UBT$_3$) with addition of Citric Acid. The exact protocol is shown in **Figure 1**.

Urea breath test (UBT)

After an 8-hours overnight fast patients were requested to swallow a 1 micro Cori urea ^{14}C capsule (HeliCap^{TM} Kibion AB Uppsala, Sweden) with 50 cc water and soon after it drink another 200 cc of water (PH=6). In the modified UBT (UBT with Citric Acid), 4 grams of Citric Acid (Merck KGaA, Germany) was added to 200 cc water which patients should drink soon after the ^{14}C-Urea capsule. After 10-15 minutes, the patient breathed out 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 to 2 minutes. Thereafter, the breath card was inserted into a small desktop Geiger Muller counter (Heliprobe Analyzer, Kibion AB, Uppsala, Sweden), and the radioactivity of the breath samples was estimated after mean 250 seconds of an automated process. Finally, the test results were expressed on the LCD of the analyzer in a numeric fashion (0: patient not infected, 1: borderline result, 2: patient infected), which corresponded to radioactivity as count per minute (CPM): <25 CPM: patient not infected, 25–50 CPM: borderline result, >50 CPM: patient infected. We considered grades 0 and 1 as negative results in our study, and only samples with activities that were more than 50 CPM (expressed as grade 2 on the counter LCD) were regarded as positive [8].

Data analysis

Demographic data of the patients were recorded in the special forms together with the results of the tests and entered the SPSS 18 software for analysis. Results were expressed as frequency distribution, and mean ± standard deviation (SD). Chi-square test was used for the comparison of false negative rates between the two parallel groups and Mc-Nemar test for the comparison of the data of two tests in one group. A *p* value less than 0.05 was defined a statistically significant difference between values.

Results

One hundred patients (54 men and 46 women) participated in the study with a mean age of 39±10.4 years (range: 18-66 years). Patients enrolled in this study were classified into two groups; 50 patients in each group. The mean age was 37.1±10.6 years in Group I and 40.7±9.9 in Group II (there was no significant difference in the view of age between two groups). **Table 1** shows the gender distribution in two groups (Chi-square test showed a homogenous distribution of genders between two groups). All the patients underwent a screening baseline ^{14}C-UBT (Heliprope). Group I showed an average ^{14}CO$_2$ excretion of 164.3±62.4 DPM (range: 60-300 DPM) in baseline UBT. While the comparable amount in group II was 180.4±79.8
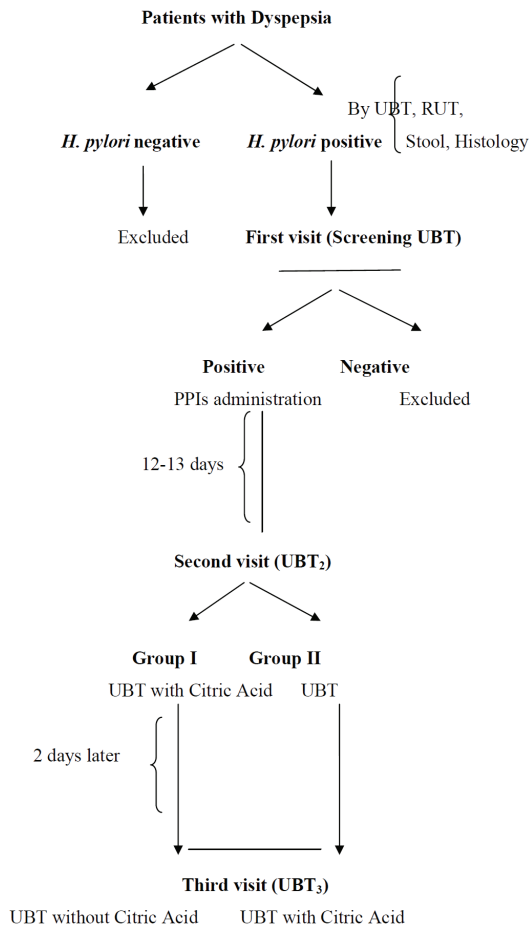
Figure 1. The protocol of the survey.

(range: 70-370) DPM. All the patients were administered PPIs (Pantoprazole) 20 mg per day.

All the patients continued the survey by undergoing two other ^{14}C-UBTs during 15 days. In group I who underwent UBT with Citric Acid in days 12-13 (UBT$_2$) and UBT without Citric Acid in days 14-15 (UBT$_3$), the results are as follow:

One individual (2%) showed negative (false negative) and 49 (98%) showed positive UBT$_2$ results in days 12-13. These patients repeatedly underwent UBT (UBT$_3$) this time without Citric Acid in days 14-15. They had 5 negative (false negative) and 45 (90%) positive results in UBT$_3$ (**Figure 2**). Mc-Nemar test showed no significant difference between false negatives of UBT$_2$ and UBT$_3$ (P=0.219). Also the difference between the baseline screening UBT and UBT without Citric Acid (UBT$_2$) was not significant (P=0.062).

In group II who underwent UBT without Citric Acid in days 12-13 (UBT$_2$) and UBT with Citric Acid (UBT$_3$) in days 14-15, the results are as follow:

From 50 patients in this group, 2 (4%) were negative (false negative) and 48 (96%) were positive in UBT$_2$, while in UBT$_3$ (with Citric Acid), one of the negative cases changed to positive and one (2%) remained negative (false negative) and 49 (98%) were positive (**Figure 3**). Mc-Nemar test showed no significant difference between false negatives of UBT$_2$ and UBT$_3$ (P=0.99). Also the difference between the results of baseline screening UBT and UBT$_2$ (UBT without Citric Acid) was not significant (P>0.5).

Discussion

Symptomatic patients referred for UBTs, prior to *H. pylori* diagnosis, often have to refrain from taking PPIs that could provide symptom relief, because of the risk of a false negative test. Previously published reports have described false negative rates of 17–38% for 20 mg/day omeprazole after 14 days and 33-61% with the use of 30 mg/day Lansoprazole. But the results on the false negative rates with Pantoprazole and rabeprazole are controversial [13, 22, 25]. Several mechanisms have been proposed to explain the ability of PPIs to induce false negative UBT results. One suggested mechanism is the inhibitory effect of PPIs for *H. pylori* [15]. McGowan *et al.* reported that PPIs inhibit *H. pylori* growth at low pH through a urease-independent mechanism suggesting a true "antibiotic" effect, perhaps as a consequence of effects on bacterial proton pumps [26]. Another possibility is that the significant increase in pH developed by many patients treated with PPIs makes the intragastric environment inappropriate for the growth of the organism (PH-dependent mechanism). The metabolic activity of Urease (an enzyme produced by *H. pylori*) provides the basis for the UBT. PPIs inhibit the Urease function. Now the question is whether acidification of the intragastric environment while UBT in patients who have taken PPIs decreases the false negative rate of the test which has been induced by PH-dependent mechanism of PPIs.

In the study by Bulbeco et al. the false negative results of ^{13}C-UBT with Citric Acid was estimat-

Table 1. The frequency distribution of gender in two groups of H. pylori *positive patients with dyspepsia*

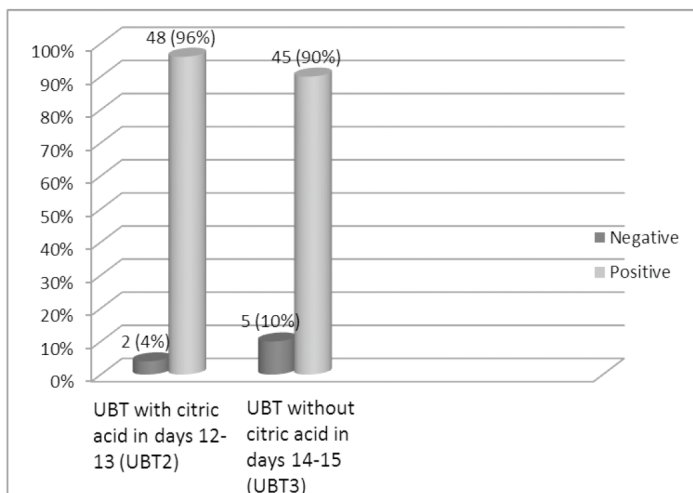| Gender	Group I N (%)	Group II N (%)
Female	25 (50)	21 (42)
Male	25 (50)	29 (58)
Total	50 (100)	50 (100)

Figure 2. The results of UBT with Citric Acid in days 12-13 (UBT$_2$) and UBT without Citric Acid in days 14-15 (UBT$_3$) in group I (P□0.05 NS).
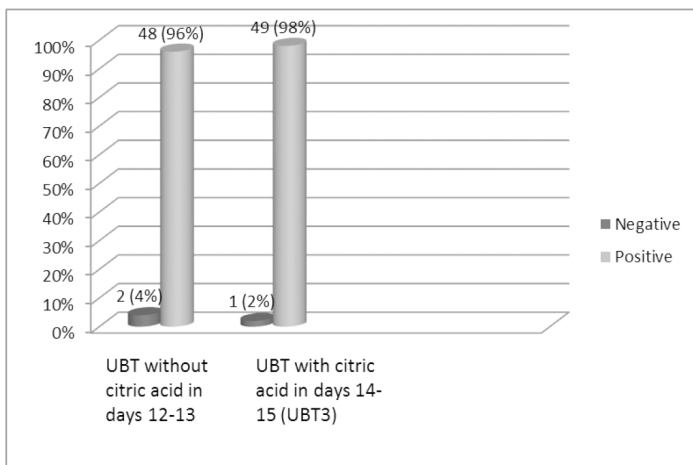

Figure 3. The results of UBT without Citric Acid in days 12-13 (UBT2) and UBT with Citric Acid in days 14-15 (UBT3) in group II (P□0.05 NS).

ed 10.7%. They also suggested that acidification of gastric environment at the time of UBT didn't have any effect on false negative rates of the test [27]. Uzturk et al. reported that the use of acidified ^{14}C-urea capsule did not prevent false negative UBT results in patients taking Pantoprazole and ranitidine, and the duration

of medication does not affect the test results [28]. Pathak et al. showed that higher acidic gastric environment (pH approx. 2.0) with Citric Acid was found to increase the exhaled $^{14}CO_2$ level in a dose-dependent manner [29]. However Dulbeco et al. reported that the long duration of Pantoprazole and Ranitidine consumption in standard doses had different effects on UBT result. It meant UBT result which was negative due to Ranitidine consumption changed positive after 30 days of the drug use [27].

Some mechanisms have been proposed for the probable increase in the amount of $^{14}CO_2$ in the breath after ingestion of ^{14}C-urea with Citric Acid. Delayed gastric emptying, pH dependent mechanisms and activating urea entry [28].

In the present survey, we performed UBT with ^{14}C radioisotope on 100 patients who were under PPIs therapy, and used Citric Acid to reduce the false negative rates. Totally among 100 dyspeptic patients, the false negative rate of ^{14}C-UBT was 7% and Citric Acid reduced the false negative to 3%. But the reduction of false negative rate following Citric Acid use was not statistically significant in Mc-Nemar test (P>0.05).

Some similar surveys have investigated the effect of PPIs on Heliprobe (with and without Citric Acid): Chey et al. 's study showed Citric Acid reduced the false negative rate of ^{14}C-UBT after PPI administration but didn't eliminate it. However, they administered Lansoprazole which induces the most false negative rate of UBT among PPIs [15]. The other survey was performed by Ozturk et al [28]. They showed a 22% false negative rate for UBT with Citric Acid. They suggested that Citric Acid consumption prevented false negative results of ^{14}C-UBT. Their administered PPI was Pantoprazole (like the present survey).

However the dose of PPI in their survey was 40 mg per day in contrary to our study (20 mg per day which is used as the standard dose). So the results of the two surveys are not comparable.

Levine et al. showed that false negative rates of ^{13}C-UBT with Citric Acid induced by various PPIs are different. They said that omeprazole and Pantoprazole induced less false negative rate while Lansoprazole and esomeprazole had high rates of false negative results [22]. However, Graham et al. showed that in patients who took omeprazole, acidification of gastric environment had no effect on reducing the false negative rate of UBT [30].

The last finding of this study is the non-significant difference between the results of the baseline UBT and UBT without Citric Acid following PPI (Pantoprazole) consumption in both groups. So we have found that the recent use of Pantoprazole didn't increase the false negative rates of the ^{14}C-UBT HELIPROBE. This is against the results of Chey et al.'s survey [15]. But the PPI which was used in that study was Lansoprazole. In the study by Levine et al. [22], treatment with Omeprazole (4.1%) or Pantoprazole (2.2%) prior to urea breath test (UBT) was associated with low false negative results, while lansoprazole (16.6%), and esomeprazole (13.6%) caused clinically unacceptable high false negative rates. These results on Pantoprazole are similar to this survey but they used ^{13}C-UBT as the diagnostic test. These observations suggest that selection of the proper test and PPIs may obviate the need to stop therapy before performing UBTs.

Of the advantages of the present survey is performing the investigation on Heliprobe (^{14}C-UBT) as a rapid convenience method for the patients. The present survey has some drawbacks too. We didn't test false negative results after withdrawal of PPIs. As mentioned above, the consumed PPI in the present survey was Pantoprazole and we don't have any idea about other PPIs. So we suggest future investigations with the larger sample size with matched groups to study the effect of different PPIs and/ or H2 receptor blockers on the UBT result individual.

Conclusion

We have found that that acidification of gastric environment while ^{14}C-UBT cannot prevent false negative results and do not increase the accuracy of the test in patients taking PPIs. Also this study has the novel finding that Pantoprazole doesn't influence the sensitivity of ^{14}C-UBT HELIPROBE at all. So maybe symptomatic patients referred for ^{14}C UBTs do not have to refrain from taking PPIs that could provide symptom relief, because of the risk of a false negative test. Other controlled clinical trials are needed to prove this finding.

Declare of conflict of interest

None.

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