Effect of gastric Acidification on the $^{14}$C-UBT HELIPROBE® accuracy during Pantoprazol treatment in Helicobacter Pylori positive patients

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Introduction
The aim of this study was to evaluate the influence of using Citric Acid on false negative rates induced by PPIs during $^{14}$C-UBT in dyspeptic patients with H.Pylori infection.

Material and Methods: 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 $H.\text{pylori}$ 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 $H.\text{pylori}$ 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 $H.\text{pylori}$ treatment and history of chronic liver and kidney diseases were excluded from the study.

This study was a crossover randomized controlled clinical trial. For all the subjects who had written consent to enter the survey, standard screening UBT (UBT1) 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 in each group). The administered PPI was 20 mg per day Pantoprazol (Pantozol® from Nycomed Company) 1/2 hour before breakfast.

Group I: Two other UBTs were performed in these patients. The first one (UBT1) was performed after 12-13 days of taking PPIs simultaneously with the administration of 4 grams Citric Acid (modified UBT) and the second one (UBT2) was performed after 14-15 days of PPIs consumption and without Citric Acid addition.

Group II: They were undertaken UBT (UBT3) after 12-13 days of PPIs consumption without Citric Acid administration and in day 14-15 (UBT4) with addition of Citric Acid. The exact protocol is shown in Figure 1.

After an 8-hours overnight fast patients were requested to drink a solution of 50 mg $^{14}$C-Urea dissolved in 10 cc water and soon after it drink another 200 cc of water (PH=6). In the modified UBT (with Citric Acid), 4 grams of Citric Acid (Merok KGAA, Germany) was added to 200 cc water which patients should drink soon after the $^{14}$C-Urea. After 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 1min to 2min. Thereafter, the breath card was inserted into a small desktop Geiger Muller counter (Heliprobe Analyser, Kibion AB, Uppsala, Sweden), and the radioactivity of the breath samples was estimated after 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 no. 2 on the counter LCD) were regarded as positive. 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 as 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: 12-66 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 (Heliprobe). Group I showed an average $^{14}$CO2 excretion of 164.3±24.2 DPM (range: 60-300 DPM) in baseline UBT. While the comparable amount in group II was 190.4±79.8 DPM (range: 70-370 DPM). All the patients were administered PPIs (Pantoprazol) 20 mg per day.

All the patients continued the survey by undergoing two other $^{14}$C-UBTs during 14 days. In group I who underwent UBT with Citric Acid in days 12-13 (UBT3) and UBT without Citric Acid in days 14-15 (UBT4), the results are as follow:

1. Individual (2%) showed negative (false negative) and 49 (98%) showed positive UBT3 results in days 12-13. These patients repeatedly underwent UBT (UBT3) this time without Citric Acid in days 14-15. They had 5 negative (false negative) and 45 (90%) positive results in UBT3 (Figure 2). Mc-Nemar test showed no significant difference between false negatives of UBT2 and UBT3 (p=0.219). Also the difference between the baseline screening UBT and UBT without Citric Acid (UBT3) was not significant (P=0.062).

In group II who underwent UBT with Citric Acid in days 12-13 (UBT2) and UBT without Citric Acid 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 UBT2, while in UBT4, 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 UBT2 and UBT4 (p=0.99). Also the difference between the results of baseline screening UBT and UBT2 without Citric Acid was not significant (P=0.5).

Totally, among all the patients who underwent UBT without Citric Acid, there were 7 false negative results, meanwhile they showed 2 false negative results when underwent UBT with Citric Acid. The difference between the total false negatives of two UBTs was not significant (P=0.136) (Table 2).

Conclusions: These results suggest that acidification of gastric environment during $^{14}$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 Pantoprazol doesn’t influence the sensitivity of $^{14}$C-UBT at all.

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

<table>
<thead>
<tr>
<th>Gender</th>
<th>Group I N (%)</th>
<th>Group II N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>25 (50)</td>
<td>21 (42)</td>
</tr>
<tr>
<td>Male</td>
<td>25 (50)</td>
<td>29 (58)</td>
</tr>
<tr>
<td>Total</td>
<td>50 (100)</td>
<td>50 (100)</td>
</tr>
</tbody>
</table>

### Table 2. Comparison of the results of UBT+Citric Acid and UBT without Citric Acid in all the patients with dyspepsia

<table>
<thead>
<tr>
<th>Results of the UBT</th>
<th>Negative</th>
<th>Positive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>UBT + Citric Acid</td>
<td>2</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>UBT without Citric Acid</td>
<td>7</td>
<td>93</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 1: The results of UBT + Citric Acid in days 12-13 (UBT2) and UBT without Citric Acid in days 14-15 (UBT3) in group I (P=0.05 NS)

Figure 2: The results of UBT + Citric Acid in days 12-13 (UBT2) and UBT without Citric Acid in days 14-15 (UBT3) in group II (P=0.05 NS)