Clinical Study

Clinical Validation of an Office-Based $^{14}$C-UBT (Heliprobe) for
$H. pylori$ Diagnosis in Iranian Dyspeptic Patients

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Background. We encountered repeatedly, in our clinical practice, discordant results between UBT and histopathology about $H. pylori$ infection. Goal. To study the diagnostic accuracy of Heliprobe $^{14}$C-urea breath test ($^{14}$C-UBT) for detection of $H. pylori$ infection in an Iranian population. Study. We enrolled 125 dyspeptic patients in our study. All of them underwent gastroscopy, and four gastric biopsies (three from the antrum and one from the corpus) were obtained. One of the antral biopsies was utilized for a rapid urease test (RUT), and three others were evaluated under microscopic examination. Sera from all patients were investigated for the presence of $H. pylori$ IgG antibodies. The $^{14}$C-UBT was performed on all subjects using Heliprobe kit, and results were analyzed against the following gold standard (GS): $H. pylori$ infection considered positive when any two of three diagnostic methods (histopathology, RUT, serology) are positive. Results. According to data analysis, the Heliprobe $^{14}$C-UBT had 94% sensitivity, 100% specificity, 93% negative predictive value (NPV), 100% positive predictive value (PPV), and 97% accuracy, compared with GS. Conclusion. The Heliprobe $^{14}$C-UBT is an easy-to-perform, rapid-response, and accurate test for $H. pylori$ diagnosis, suitable for office use.

1. Introduction

$Helicobacter pylori$ ($H. pylori$) is a spiral shaped microaerophilic gram-negative bacterium that resides in the gastric epithelial mucosa and induces an inflammatory response leading to gastritis and peptic ulcer disease [1, 2]. It has been implicated as playing a role in gastrointestinal malignancies, especially gastric adenocarcinoma and MALToma until the latter could be treated with $H. pylori$ eradication [3, 4].

$H. pylori$ has a worldwide prevalence rate of about 50%, with a higher prevalence in developing countries [5, 6]. According to population-based studies, it has been shown that the $H. pylori$ infection rate is very high in the Iranian population [7].

$H. pylori$ detection can be made with diverse diagnostic tests, which are technically divided into invasive and noninvasive based on whether endoscopy is required or not. Invasive tests offer the possibility of obtaining tissue samples, which can be used for a rapid urease test (RUT), culture, polymerase chain reaction (PCR), and histopathologic evaluation. Noninvasive tests include serum $H. pylori$ IgG antibody titer, the urea breath test (UBT), and $H. pylori$ stool antigen assay. Compared to noninvasive diagnostic modes, however, invasive techniques are inconvenient for patients and also have higher cost [8].

A UBT diagnostic test is based on the fact that swallowed “labeled carbon-containing urea” is broken down to ammonia and carbon dioxide ($CO_2$) by the urease-producing microorganism ($H. pylori$) in the gastric mucosa, and, finally, tagged carbon within the liberated $CO_2$ is detected in exhaled breath samples [9, 10].

Between two carbon isotopes ($^{13}$C and $^{14}$C), which are used for the UBT, the $^{13}$C isotope has the difficulty of requiring more complex equipment, such as a mass spectrophotometer and administration of a pretest meal such as citric acid. However, when the $^{14}$C isotope is utilized, the required equipment is only a portable compact beta-scintillation counter, which offers the convenience of performing the test...
in the office. Although the $^{14}$C isotope is radioactive, micro-
dose (1 µCi) $^{14}$C has the minimal radiation of one day back-
ground exposure [11].

We encountered repeatedly, dyspeptic patients, in our
clinical practice, whose UBT results were not consistent with
histopathology about H. pylori infection; based on Helici-
obacter genetic polymorphisms and differences between H.
pylori strains in different countries, and since clinical valida-
tion of Heliprobe $^{14}$C-UBT has not yet been investigated in
an Iranian population, we conducted a prospective study to
compare Heliprobe $^{14}$C-UBT performance against diagnostic
gold standards [12–14].

2. Materials and Methods

We studied 125 consecutive patients with dyspepsia that had
been referred for upper Gl endoscopy. We defined dyspepsia,
based on the Rome III criteria, as having one or more of
the following conditions: postprandial fullness (termed
postprandial distress syndrome), early satiation (inability
to finish a normal-sized meal or postprandial fullness),
and epigastric pain or burning (termed epigastric pain
syndrome) [15].

We considered subjects aged 15 y–75 y. We excluded
patients who had been using proton pump inhibitors, H2
blockers, or any antibiotics within four previous weeks of the
diagnosis, as having one or more of the following condi-
tions: postprandial fullness (termed postprandial distress
syndrome), early satiation (inability to finish a normal-sized
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We considered subjects aged 15 y–75 y. We excluded
patients who had been using proton pump inhibitors, H2
blockers, or any antibiotics within four previous weeks of the
diagnostic method. Pregnant women, patients who had
a history of H. pylori eradication, and those with any severe
heart conditions were excluded as well. Study personnel
were blinded as to patient test results. The study protocol was
approved by the ethics committee of the Gastrointestinal
and Liver Diseases Research Center of Guilan University
of Medical Sciences, and written informed consents were
obtained from each participant.

After an overnight fast, patients underwent gastroscopy
with a FUJINON endoscope, and four separate gastric
biopsies were taken, three from the antrum and one from the
corpus. One of the antral samples was used for a rapid urease
test (RUT), and two antral samples plus the corpus biopsy
sample were used for histopathologic examination.

To perform the RUT, we utilized a home-made liquid
rapid urease kit (Gastric Urease, Bahar Afshan Co., Iran). We
put tissue samples in a yellow-colored reagent liquid,
and results were read after 30 min, 60 min, and finally after
24 hours. Liquid color changes into deep red, purple, or vio-
et indicated a positive result. Negative results were indicated
by no color change. Tissue samples were prepared with stan-
dard hematoxylin and eosin (H&E) and Giemsa stainings
for histopathologic investigation. The histopathology exam
result was considered positive when H. pylori was detected in
either of the stains and negative when the organism was not
detected in any.

One blood sample was obtained from each patient
to be examined for anti H. pylori IgG titer. We utilized
the ELIZA method (LDN, Nordhorn, Germany), and sera
with titers that were >11 international units (IU) were
considered positive (test cut-off point: 10 IU, <9 IU: negative,
9–11 IU: doubtful, >11 IU: positive); we regarded doubtful
results as negative.

After gastroscopy, we performed Heliprobe $^{14}$C-UBT
tests. In order to carry out the UBT, after an overnight
fast, the patient swallowed a $^{14}$C-labeled urea-containing
capsule (Helcap, Institute of Isotopes, Budapest, Hungary)
with water. The overall activity of these capsules is as small
as 1 µCi (37 KBq). 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 1 min to 2 min. Thereafter, the breath card
was inserted into a small desktop Geiger Müller counter
(Heliprobe Analyser, Kibion AB, Uppsala, Sweden), and
the radioactivity of the breath samples was read 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 in-
fected), 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.

Descriptive analysis was done for demographic features.
Gold standard for H. pylori positivity was defined as “positive
results for any two of three diagnostic methods (histopathol-
yogy, RUT, serology).” Sensitivity, specificity, negative and
positive predictive values (NPV and PPV), and the accuracy
of the UBT were computed against our GS; for categorical
variables, 95% confidence interval (95% CI) was calculated.

3. Results

We enrolled 125 consecutive patients in our study according
to the above mentioned inclusion and exclusion criteria; 65
(52%) were females, and 60 (48%) were males. Patient ages
ranged from 18 y to 66 y with a mean of 35.81 ± 12.97 y.

As a result of histopathologic evaluation of tissue spec-
imens, 69 (55.2%) patients were found to be infected with
H. pylori, and 56 (44.8%) were not infected. Serologic
examination of patient sera samples for IgG antibody against
H. pylori showed 87 (69.6%) positive results, while the
remaining 38 (30.4%) were seronegative. The RUT results
were positive in 63 (50.4%) patients and negative in 62
(49.2%) patients. H. pylori infection was found in 67 (53.6%)
subjects by the $^{14}$C urea breath test ($^{14}$C-UBT), and 58
(46.4%) subjects were negative.

All four tests were positive or negative in 57 (45.6%)
and 34 (27.2%) patients, respectively. Only 2 patients had
no histopathologic evidence of H. pylori infection, whilst
their RUT and serology results were positive. (Incidentally
these two patients also had positive UBTs.) We think that
this might be the result of errors during sampling or
histopathologic examination. 20 patients showed solitary
positive serology tests which indicated recent past infection.
Table 1 shows other discordances between our test results.
84% NPV, and 94% accuracy [19]. Our results are also in accordance with Ozdemir et al. that is again regarding only histopathology as GS, Heliprobe had higher sensitivity (100%), but its specificity (76%) was lower than that of our study [22].

People who undergo medical diagnostic tests using radioisotopes are often worried about radiation exposure. The half life of the 14C isotope is about 5000 years, but, with regards to the short biologic half life of urea, more than two-thirds of the tagged urea will be excreted in the urine within the following three days of the test; moreover, the total dose of the 14C used in the test is very low, and activity of this quantity of isotope was evaluated as 1 µCi. Accordingly, based on the published data, about 800 breath testing episodes must be carried out for one person to receive an effective dose equivalent to the amount that an average person absorbs from natural sources in one year [23]. Considering the few times a person needs to be tested with the 14C-UBT, the lifelong cumulative radiation of the test is negligible. Even in conditions of repeated UBT testing, radiation exposure risk is very low. Previously, 14C-UBT was not used in children because of the concerns about the radiation hazards; however, diverse studies have established its safety in pediatric patients [11, 24]. Although no experimental study has yet been done to assess 14C-UBT safety in pregnancy, Bentur et al. have claimed that, in view of the insignificant 14C radioactivity, fetal radiation exposure is extremely lower than teratogenic thresholds [25].

One of the advantages of the Heliprobe system is that it can be used in a clinical setting, allowing the preparation of test results on-site in less than one hour. The portable beta-scintillation counter that is used in this test could simply be placed on a desktop; however, the 13C-UBT needs a sophisticated mass spectrophotometer to read the results. Of course, 13C-UBT has some advantages over 14C-UBT such that the former utilizes a nonradioactive isotope that makes it suitable to use in pregnant women and children. Although some studies, as mentioned earlier, have already emphasized on 14C-UBT safety in children, 13C-UBT is still the preferred method in them. Considering 13C safety, it is also a better choice than 14C for epidemiologic studies, as some studies used it to investigate H. pylori routes of transmission in preschool age [26, 27].

Stool antigen is another sensitive and specific noninvasive diagnostic test for H. pylori [28]. Although it is competitive with the 14C-UBT in terms of accuracy, but it is not appropriate for office use because it is a time consuming exam regarding sampling limitations and off-site test interpretation.

Conclusively, compared to invasive gold standards, the Heliprobe 14C-UBT is an accurate, sensitive, and specific test for H. pylori diagnosis. The main advantages of the Heliprobe 14C-UBT are its rapidity and patient convenience. Furthermore, in view of the very low radioactivity of the Heliprobe 14C-UBT and its portability, this test seems to be a more suitable option for office use than a nonradioactive, complex and off-site 13C-UBT as well as other invasive diagnostic modalities.

Table 1: Distribution of H. pylori diagnostic test discordant results.

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Histology</th>
<th>RUT</th>
<th>Serology</th>
<th>UBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>57</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>−</td>
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<td>20</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>34</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

RUT: rapid urease test; UBT: urea breath test; +: positive; −: negative; n: number.
Table 2: Diagnostic performance of Heliprobe 14C-UBT against gold standard.

<table>
<thead>
<tr>
<th>Gold standard</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>Accuracy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14C-UBT</td>
<td>94% (85–98%)</td>
<td>100% (92–100%)</td>
<td>100% (93–100%)</td>
<td>93% (82–98%)</td>
<td>97%</td>
</tr>
</tbody>
</table>

14C-UBT: urea breath test with labeled carbon-14; RUT: rapid urease test; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval. For gold standard definitions refer to the text.

Conflict of Interests

There are no potential conflict of interests that any of the authors have identified relevant to this paper.

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References


