Validity and cost comparison of 14 carbon urea breath test for diagnosis of H Pylori in dyspeptic patients

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1 author:

Shahid Rasool
The University of Faisalabad
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RAPID COMMUNICATION

Validity and cost comparison of ^{14}carbon urea breath test for diagnosis of *H Pylori* in dyspeptic patients

Shahid Rasool, Shahab Abid, Wasim Jafri

Shahid Rasool, Shahab Abid, Wasim Jafri, Section of Gastroenterology, Department of Medicine, The Aga Khan University Hospital, Karachi, Pakistan.
Supported by University Research Council Grant, No. 041F431YC
Correspondence to: Dr. Shahab Abid, MBBS, FCPS, Associate Professor, Department of Medicine, Aga Khan University Hospital, Stadium Road, Karachi, Pakistan. shahab.abid@aku.edu
Telephone: +92-21-4864656 Fax: +92-21-4934294
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Abstract

AIM: To validate and compare the cost of microdose ^{14}C urea breath test (UBT) with histology and rapid urease test for the diagnosis of *H Pylori*.

METHODS: Ninety-four consecutive patients with dyspeptic symptoms undergoing gastroscopy were enrolled. Gastric biopsies were taken for histology and rapid urease test. UBT was performed after gastroscopy by microdose ^{14}C urea capsules. Sensitivity, specificity and accuracy of UBT were calculated and compared with histology and rapid urease test. Cost comparison of these tests was also performed.

RESULTS: *H pylori* was diagnosed by histology and rapid urease test in 66 (70%) and 61 (65%) patients, while ^{14}C UBT detected infection in 63 (67%). Accuracy of UBT was 93% in comparison with histology while its positive and negative predictive values were 97% and 84%, respectively. Comparison of ^{14}C UBT with rapid urease test gives an accuracy of 96%, with positive and negative predictive values of 95% and 97%, respectively. These results were highly reproducible with a Kappa test (P value < 0.001). Cost of histology or rapid urease test with gastroscopy was 110 USD or 95 USD respectively while the cost of UBT was 15 USD.

CONCLUSION: Microdose ^{14}C UBT was comparable to histology and rapid urease test. ^{14}C UBT is an economical, self sufficient and suitable test to diagnose active *H pylori* infection in less developed countries.

Key words: *H pylori*; Microdose; ^{14}C urea breath test; Diagnosis; Reliable; Economical

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INTRODUCTION

H Pylori is a gram negative, microaerophilic human pathogen which is prevalent worldwide. *H Pylori* infection causes gastritis and is associated with development of peptic ulcer disease, gastric carcinoma, lymphoma, micronutrient deficiencies and ischemic heart disease[1,2]. The International Agency for Research on Cancer classified *H Pylori* as group 1 carcinogen (a definite cause of cancer in humans)[3].

H Pylori can be diagnosed by invasive techniques requiring endoscopy and biopsy such as histology, tissue culture and detection of *H Pylori* by polymerase chain reaction. The non-invasive techniques for the diagnosis of *H Pylori* include serum *H Pylori* antibody titer, urea breath test (UBT) and *H Pylori* stool antigen test. A reliable, non-invasive and economical diagnosis is a best choice for the management of *H Pylori* in both test and treatment.

Among the non-invasive tests, UBT is supposed to be a gold standard test for the diagnosis of *H Pylori* infection. UBT is based on enzymatic hydrolysis of labeled urea in the stomach by urease, an enzyme produced in abundance by *H Pylori*. In the presence of *H Pylori* infection, urea is hydrolyzed to ammonia and carbon dioxide (CO_2). This labeled CO_2 is exhaled and measured for radioactivity. Bacteria other than *H Pylori* that produce urease in a small amount cannot survive in the gastric mucosa.

There are two types of UBT, ^{13}C UBT and ^{14}C UBT. The former is difficult to analyze because it requires sophisticated infrastructure such as a mass spectrometer, technical expertise and therefore costly while ^{14}C UBT is an easily available technique that uses ^{14}C urea capsules with a 5, 3 or 1 uCi dose. The microdose 1 uCi (Helicap) utilizes a very low dose of radiation[4,5]. Considering these facts, in 1997 the Nuclear Regulatory Commission permitted *in vivo* diagnostic use of capsules containing 1 uCi of ^{14}C urea without a license[6]. The equipment is small, portable and can be placed on a desktop. Microdose ^{14}C UBT is claimed to be a reliable and economical diagnostic test for *H Pylori* infection, which may be used even in remote areas with limited resources.

This prospective study was done to determine the validity and cost of microdose ^{14}C UBT in comparison with histology and rapid urease test for the diagnosis of *H Pylori*.

MATERIALS AND METHODS

All consecutive men and non-pregnant women with dyspeptic symptoms undergoing gastroscopy were considered for enrollment.

Dyspepsia was defined as the presence of one or more of the postprandial fullness, early satiation, or epigastric pain or burning for the last three months with symptom onset at least six months before diagnosis according to the latest Rome Ⅲ criteria[7].

Inclusion criteria

Patients of both genders with dyspepsia were 18-70 years in age. Patients with a history of recent intake of proton pump inhibitor and antibiotics were enrolled only if four weeks have passed since last systemic antibacterial or bismuth medication therapy and 1 wk since last use of proton pump inhibitor or H2-receptor antagonist.

Exclusion criteria

Pregnant women, patients who had gastric surgery, patients with a history of *H Pylori* eradication therapy in the past six months and patients with active gastrointestinal bleeding were excluded from the study.

Ethical clearance

Study protocol was approved by the institutional ethical review committee. Written informed consent was obtained from all patients before enrollment.

Endoscopy and biopsy sampling

After overnight fast, esophago-gastro-duodenoscopy was performed with Olympus or Pentax videoscope. Six biopsies were taken, three from antrum and other three from the body of stomach from each patient. Two biopsies, one from the antrum and the other from the body were used for rapid urease test and the other four (two from antrum and two from body) for histology.

Rapid urease test

Rapid urease test kit (Pronto Dry, Medical Instrument Corp., France) was used to detect the presence of *H Pylori* urease[8]. Result was read in 30 min and 1 h after sampling. The color change from yellow to pink was considered positive and no color change as a negative result. Results were interpreted by either endoscopist or his assistant who were blinded about the results of UBT and histology.

Histology

Four biopsy specimens (two from corpus and two from antrum) were processed separately for histological examination according to standard procedure. Hematoxylin and eosin (HE) and Giemsa staining was performed on these samples. Results were interpreted by a pathologist who was blinded about the results of UBT and rapid urease test. Pathologist commented on the active and chronic *H Pylori* infection based on the presence of *H Pylori* along with neutrophils, eosinophils, lymphocytes, lymphoid follicles, and intestinal metaplasia according to the classification by Genta RM *et al*[9].

^{14}C UBT

Patients swallowed 37 kBq (1 uCi) of an encapsulated form of ^{14}C-urea/citric acid composition (Helicap, Noster System AB Stockholm, Sweden) with water after endoscopy. Breath samples were collected with a special dry cartridge system (Heliprobe Breath Card, Noster System AB Stockholm, Sweden) after 10 min. Patients exhaled gently into the cartridge mouthpiece until the indicator membrane changed in color from orange to yellow. Breath card was inserted into a β-scintillation counter (Heliprobe-analyser, Noster System AB Stockholm, Sweden) and activity was counted for 250 s. This is a portable machine that can be placed on a desktop. Results were expressed both as counts per minute (HCPM) and as grade (0: not infected, CPM < 25; 1: equivocal, CPM 25-50; 2: infected, CPM > 50), which was suggested by the producer according to the counts obtained from the cartridges[10]. Grades 0 and 1 were considered negative for the detection of *H Pylori*.

Statistical analysis

The statistical package for social science SPSS (release 11.5, standard version, copyright © SPSS) was used for data analysis. The descriptive analysis was done for demographic features. Results were presented as mean ± SD in number (percentage).

Sensitivity, specificity, positive and negative predictive values of UBT with 95% confidence intervals were calculated against histology and rapid urease test. Kappa test was applied to check the reproducibility of the results. Cost comparison of these diagnostic methods was also performed.

RESULTS

Ninety-four consecutive patients with dyspeptic symptoms undergoing gastroscopy were enrolled for the validity of microdose ^{14}C UBT. There were 60 (64%) men and the mean age of study group was 40.8 ± 12.8 years. *H Pylori* infection was diagnosed by histology in 66 (70%) patients and by rapid urease test in 61 (65%) patients. UBT detected active *H Pylori* infection in 63 (67%) patients. Demographic characteristics of the patients and results of these diagnostic tests are summarized in Table 1.

^{14}C UBT vs histology

In comparison with histology, UBT has a sensitivity and specificity of 92% (95% CI: 87%-95%) and 93% (95% CI: 79%-99%), respectively. The positive predictive value (PPV) of ^{14}C UBT was found to be 97% (95% CI: 91%-99%) and negative predictive value (NPV) was 84% (95% CI: 72%-89%) compared with histology. These results show that UBT has an accuracy of 93% as compared with

Table 1 Patient demographics and results of *H Pylori* detection by various tests (n = 94), mean ± SD

Parameters	n (%)
Gender	
Male	60 (64)
Female	34 (36)
Age (yr)	40.8 + 12.8
Histopathology	
Positive	66 (70)
Negative	28 (30)
UBT	
Positive	63 (67)
Negative	31 (33)
Rapid urease test	
Positive	61 (65)
Negative	33 (35)

histology. Kappa test result was 0.805 with P value < 0.001, indicating that these results were reproducible (Table 2).

^{14}C UBT vs rapid urease test

In comparison of UBT and rapid urease test, the sensitivity and specificity of UBT were 98% (95% CI: 93%-99%) and 91% (95% CI: 80%-94%). The PPV and NPV were 95% (95% CI: 89%-97%) and 97% (95% CI: 86%-99%), respectively. UBT has an accuracy of 96% in comparison with rapid urease test. Result of Kappa test was 0.881 ($P \leqslant 0.001$) which showed a good response (Table 2).

Four patients with histological evidence of *H Pylori* infection had negative results with UBT and rapid urease test. The discordant results between histology, UBT and rapid urease test are shown in Table 3.

Cost analysis

At the time of this study, the cost of gastroscopy was 90 USD while the cost of histology and rapid urease test was 20 USD and 5 USD in our institute. Therefore, the overall cost of *H Pylori* diagnosis by histology was 110 USD and 95 USD by rapid urease test. The cost of UBT was only 15 USD in our institute.

DISCUSSION

Current guidelines for the management of *H Pylori* infection recommend eradication treatment without performing endoscopy in patients under 45 years of age who have no remarkable symptoms[11-13]. The use of non-invasive tests has been advocated in different strategies for management of dyspeptic patients in the primary care based on clinical and economical analyses[14,15].

Invasive diagnostic tests for *H Pylori* diagnosis need gastroscopy that requires sedation and monitoring during the procedure by trained staff and expertise. These diagnostic tests are costly and require an established healthcare infrastructure.

In practical terms, invasive tests for the diagnosis of *H Pylori* are not feasible, especially in less developed countries. An economical, reliable and office based diagnostic test is therefore, more appropriate in settings of

Table 2 Sensitivity and specificity of ^{14}C UBT against histopathology and rapid urease test for *H Pylori* diagnosis (n = 94)

UBT compared to:	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy
Histopathology	92% (87-95)	93% (79-99)	97% (91-99)	84% (72-89)	93%
Rapid urease test	98% (93-99)	91% (80-94)	95% (89-97)	97% (86-99)	96%

UBT: urea breath test; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval.

Table 3 Discordant results between histopathology, ^{14}C UBT and rapid urease test for *H Pylori* diagnosis (n = 94)

Groups	Patients (n)	Histopathology	UBT	RUT
Group 1	59	+	+	+
	2	+	+	-
	1	+	-	+
	4	+	-	-
Group 2	1	-	+	+
	1	-	+	-
	26	-	-	-

UBT: urea breath test; RUT: rapid urease test; +: positive; -: negative.

under privileged and cost constraint societies.

Other factors that determine choice of diagnostic tests apart from accuracy, in primary care setting include the availability of test, ease to perform, cost, self-sufficiency and acceptance by the patients. Present study has shown that microdose ^{14}C UBT has all these features.

Our study has demonstrated a high accuracy of microdose ^{14}C UBT for the detection of *H Pylori* infection comparable to histological diagnosis of *H Pylori*. The results of present study are comparable to other studies, with a sensitivity and specificity of more than 90% for the diagnosis of *H pylori* infection[16-18].

The sensitivity and specificity of ^{14}C UBT were 98% and 91% while PPV and NVP were 95% and 97% respectively, compared with rapid urease test. The overall accuracy was 96%. These results are similar to another study that found a 93% sensitivity, 96% specificity and 95% accuracy in comparison with rapid urease test[19]. Moreover, studies using a combination of histopathology and rapid urease test as a gold standard has also reported a comparable sensitivity and specificity of ^{14}C UBT above 90%[20,21].

H Pylori Stool Antigen (HpSA) test is a promising non-invasive test. This test seems to be equivalent to the UBT in terms of its yield of diagnosing *H Pylori*[22]. However, collection of stools may be a disagreeable task for many patients and it is difficult to manage in office based settings. *H Pylori* serum antibody test is another non-invasive test. It has a low sensitivity and specificity and it does not indicate active *H Pylori* infection because antibody titers can remain high for a long period despite adequate treatment[23]. It is one of the best tests for estimation of sero-prevalence of *H Pylori*, unfortunately it is not an ideal

test for the diagnosis of active *H Pylori* infection.

It has been shown that UBT becomes false negative during treatment with proton pump inhibitors and H-2 blockers[24,25]. However, it has been observed recently that addition of citric acid in the urea capsule may diminish the negative effect of acid inhibitory drugs on the accuracy of ^{14}C UBT[26]. Although we used an acidified ^{14}C urea capsule (Helicap), we preferred to discontinue anti-acid medications for at least seven days before the test. Controversies exist regarding the best diagnostic test for *H Pylori* among patients with active upper GI bleeding. ^{13}C UBT was found better than histology and rapid urease test by a few studies in patients with active upper GI bleeding[27,28]. However, validity of ^{14}C UBT in patients with active upper GI bleeding has never been assessed.

Concerns about the radiation hazard can be raised against ^{14}C UBT. However, it has been found in practice that by using microdose ^{14}C UBT, only a small amount of isotope was used and the test actually entailed low radiation exposure (3 mSv)[29,30].

Nearly the entire ingested isotope is rapidly excreted in urine or breath within 72 h. Recently safety of microdose ^{14}C UBT has been established even in young children[31].

In conclusion, microdose ^{14}C UBT is a highly sensitive and specific non-invasive test comparable to the invasive methods such as histology and rapid urease test used for *H Pylori* diagnosis. This test requires no sophisticated infrastructure. ^{14}C UBT is self-sufficient and easy to perform with readily available results. In our opinion, this is one of the best options for detection of *H Pylori* infection in office based settings, especially in less developed countries.

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COMMENTS

Background

H pylori is one of the most prevalent infection organisms, especially in low socio-economic societies. It is associated with intestinal and extra-intestinal manifestations including malignancy. There is a need to establish cost-effective eradication strategies especially in less developed countries.

Research frontiers

Microdose ^{14}C Urea Breath Test (UBT) is carried out without the use of sophisticated equipment and specialized trained personnel. There is a need to compare the diagnostic usefulness of ^{14}C UBT with other diagnostic modalities such as histopathology and rapid urease test for *H pylori* detection. This comparison will help establish the value of ^{14}C UBT in resource constraint settings.

Innovations and breakthrough

^{14}C UBT is not a commonly used diagnostic method and there are only few studies about the accuracy of ^{14}C UBT for *H pylori* diagnosis. This study concluded that the sensitivity and specificity of microdose ^{14}C UBT is comparable to mostly used invasive diagnostic tests, such as histopathology and rapid urease test.

Application

Microdose ^{14}C UBT may be utilized for the non-invasive diagnosis of *H pylori* especially in the areas lacking an established health care structure. It can be used in accordance with the "test and treatment" policy in patients with dyspepsia without remarkable features.

Terminology

Dyspepsia is defined as the presence of one or more symptoms of the postprandial fullness, early satiation, epigastric pain or burning for the past three months with symptom onset at least six months before the diagnosis according to the latest Rome Ⅲ criteria. ^{14}C UBT is available in 5, 3 and 1 uCi dose. The microdose 1 uCi (Helicap) utilizes a very low dose of radiation.

Peer review

This is an interesting paper which addresses an important issue in the diagnosis of *H pylori* infection. Authors reported that the microdose ^{14}C UBT is a simple, less expensive and accurate test to diagnose *H pylori* infection. The paper is well written and conclusions are supported by results.

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