

What is the Best Method to Diagnose *Helicobacter* Infection in Bleeding Peptic Ulcers ? : A Prospective Trial

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Background : *It has been debated which diagnostic test should be preferred for the diagnosis of Helicobacter pylori (HP) in patients with peptic ulcer diseases. Several limitations are reported in bleeding peptic ulcers because of intragastric blood and possibility of changed numbers of organisms by medication. This study was designed to find out the best method for diagnosis of HP infection, in aspect of deciding the times of detection and the specific tests in bleeding peptic ulcers.*

Methods : *We prospectively examined histology, rapid urease test (CLO test), urea breath test (¹³C-UBT) and serology in HP diagnostics in 32 patients with bleeding peptic ulcers to detect HP infection. Each test was performed two times (four methods at first 24 hours and former three methods at 7th day after initial therapeutic endoscopy). We evaluated the sensitivity of each test, compared the two-times results and evaluated the effect of these tests to an outcome of endoscopic hemostasis.*

Results : *Diagnostic sensitivities of histology, CLO test, ¹³C-UBT and serology are 75%, 67.8%, 100% and 100% at first endoscopy, and 71.4%, 78.5%, 89.3% at 7th day endoscopy, respectively. Histologic study and CLO test had diagnostic limitation at emergent first endoscopy contrary to UBT (p<0.01). Histologic study, CLO test and UBT have limitations at 7th day endoscopy. Only 3 patients (9.4%) rebled with subsequent complete endoscopic hemostasis and all diagnostic tests at initial endoscopy did not influence the outcome of hemostasis.*

Conclusion : *First day histologic and CLO tests are inadequate methods in detecting HP infection in patients with bleeding peptic ulcers. 7-day histologic, CLO test and UBT have a low sensitivity. First-day UBT can be a standard test to diagnose HP infection in patients with bleeding peptic ulcers.*

Key Words : *Bleeding peptic ulcer, Helicobacter pylori, Urea breath test*

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INTRODUCTION

Helicobacter pylori (HP) has been strongly associated with peptic ulcers and it is thought to be a main etiologic

factor in peptic ulcer disease¹⁻⁶. The eradication of HP prevents recurrent bleeding in bleeding peptic ulcers⁷⁻¹⁵. Since several studies have reported that prevalence rate of HP infection may be underestimated in patients with bleeding peptic ulcers, it is debated that multiple tests or methods should be preferred for the diagnosis of HP in patients with bleeding peptic ulcer diseases^{9, 16-19}. Although various diagnostic tests are introduced with their own efficient outcomes, several limitations as diagnostic tests are reported in bleeding peptic ulcers because of intragastric blood and possibility of changed numbers of organisms by anti-ulcer medication¹⁹⁻²². This study was designed to find out the best method for diagnosis of HP infection, in aspect of deciding the times of detection and the specific tests in bleeding peptic ulcers. We wanted to evaluate the validity that noninvasive test can execute a diagnostic role in bleeding peptic ulcers.

MATERIAL AND METHODS

Patients selection and characteristics

From September 1998 to July 1999, we prospectively tried tests two times (first 24 hrs and 7th day after initial therapeutic endoscopy) for 32 patients of bleeding peptic ulcers to detect HP infection by histologic study, rapid urease test (CLO test), carbon 13 labeled urea breath test (UBT) and serologic examination. We evaluated the sensitivity of each test, compared the two-times results and evaluated the effect to an outcome of endoscopic hemostasis.

We excluded the patients who has taken anti-ulcer medication or antibiotics or nonsteroidal antiinflammatory drugs (NSAIDs) before admission. Clinical features and endoscopic characteristics are recorded from each patient. Each patient or relative gave his or her written consent before the test and therapeutic endoscopy was performed. The test and treatment protocol had been approved by the Ethics Committee of the Soonchunhyang University Hospital (Chonan, Republic of Korea).

Diagnostic methods

During endoscopy, at first we performed endoscopic hemostasis by hemoclipping and/or hypertonic saline epinephrine (HSE) injection. After we confirmed initial hemostasis, we performed a multiple test for HP infection, including rapid urease test (CLO test, Ballard, Australia),

which was observed for up to 24 hours, and histologic examination from endoscopic biopsy, ¹³C-labeled UBT and serologic examination for the presence of immunoglobulin G (IgG) antibody to HP (*Helicobacter pylori* IgG, Radim, Italy).

After initial endoscopic hemostasis, a total of 4 biopsy specimens were obtained as two sets of antrum and body regardless of the presence of intragastric blood and one set of antrum and body was used for the CLO test and monitored for color change for up to 24 hours at room temperature. Another set was sent to an experienced pathologist for histologic examination with routine and special stains (modified Giemsa or Warthin-Starry silver stain).

After endoscopic hemostasis and aninvasive diagnostic test, we performed the ¹³C-UBT. The test consisted of a baseline breath sample and second breath sample collected 15 minutes after oral administration of 75 mg of ¹³C-labeled urea (HelikitTM, Isotechnica Inc, Canada) dissolved in tap water. If the value of the carbon dioxide expired in both samples differed by more than 4 per mil, this was considered a positive result.

The blood sample for serologic evaluation was obtained before any medication was begun. An enzyme-linked immunosorbent assay for IgG antibody to HP was performed with a cutoff of 30 UR/mL. It was suggested by the manufacturer.

Criteria for second study

Through the first-day study, the patients who had two or more positive results among multiple tests (CLO test, histologic examination, UBT and serologic examination) were included. We did not exclude patients with rebleeding to evaluate the safety of the diagnostic test. Patients were carefully observed and given follow-up treatment through histamine-2 receptor antagonists (ranitidine, 50 mg intravenously every 6 hours), antacid and antemorrhagic drugs. However, we avoided other medicine or procedure which affect HP concentration of the stomach. At 7th day after initial study, we repeated the multiple test, except the serologic examination, for HP infection through the same methods as the first-day study.

Statistical analysis

The sensitivity of each test for HP infection was calculated. To assess whether each test was statistically different in sensitivity between the two day studies, Fisher's exact or Chi-square test was used. Chi-square test was performed to evaluate the difference in sensitivity between the CLO test and the ¹³C-UBT.

RESULTS

Sensitivity of diagnostic tests

Diagnostic sensitivities of histologic study, CLO test, UBT and serologic examination were 75% (24/32), 68.8% (22/32), 100% (32/32), 100% (32/32) at first endoscopy, respectively, and those of the former three tests were 71.9% (23/32), 78.1% (25/32), 90.6% (29/32) at 7th day endoscopy.

Comparison of diagnostic test sensitivities

The sensitivities of the histologic study and CLO test were significantly lower than other tests (UBT or serologic examination) at first day study ($p < 0.01$, Figure 1). Histologic, CLO, and UBT have limitations at 7th day endoscopy (Figure 2).

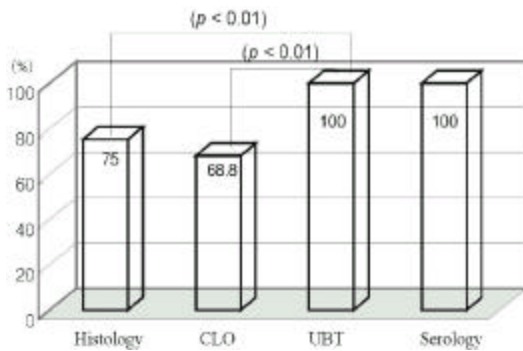


Figure 1. This figure shows the comparison of diagnostic sensitivities at first day. The sensitivities of the histologic study and CLO test were significantly lower than other tests (UBT or serologic examination) ($p < 0.01$).

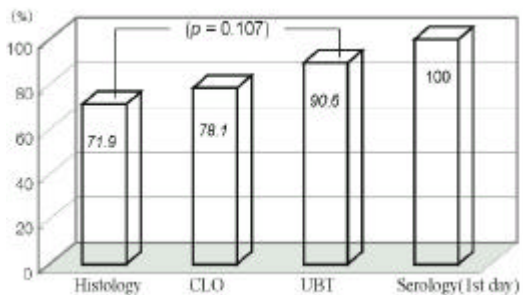


Figure 2. This figure shows the comparison of diagnostic sensitivities at 7th day. Histologic, CLO and UBT have limitations to detect HP infection. Sensitivity of UBT has a tendency of being higher than histology ($p = 0.107$).

The sensitivities of the UBT had a tendency of decrease at examination of 7th day ($p = 0.238$), and sensitivity of the CLO had a tendency of increment at examination of 7th day ($p = 0.199$) (Figure 3).

The sensitivity of the diagnostic test according to the site of the lesion was not statistically different (Table 1).

As outcomes of endoscopic hemostatic treatment, initial hemostasis rate was 93.8% (30/32), rebleeding rate was 9.4% (3/32) and operation rate was 6.2% (2/32). 3 rebleeding patients were completely controlled by subsequent complete endoscopic hemostasis. All diagnostic tests at initial endoscopy did not influence the outcome of hemostasis compared to our previous result for hemostatic efficacy in bleeding peptic ulcers²⁰.

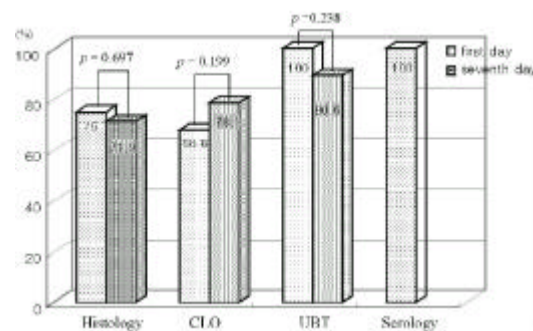


Figure 3. This figure shows the comparison of diagnostic sensitivities between 2-times study. The sensitivity of the UBT has a tendency of decrease at examination of 7th day, and sensitivity of the CLO has a tendency of increment at examination of 7th day.

Table 1. Sensitivity of Diagnostic Tests According to Site of Lesion

	Gastric ulcer (n=21)		Duodenal ulcer (n=11)	
	First	Seventh	First	Seventh
Histologic study	70	65	81.8	90
CLO test	60	70	90.9	87
UBT	100	75	100	80

CLO; Campylobacter-like organism,

UBT; Urea breath test

DISCUSSION

There is still no established gold standard for the diagnosis of HP infection. The choice of diagnostic

modality to determine HP infection status depends on test availability, ease of use, HP treatment history and whether esophagogastroduodenoscopy is planned. It has been debated which diagnostic test should be preferred for the diagnosis of HP in patients with peptic ulcer diseases. There are many presumable limitations of various diagnostic tests, which include changes of urease activity, changes of pH in sample or test medium, changes of number of HP organism, cost, time consumption, technical personal effort, clinical state of patients and patient's preference. Intra-gastric blood and possibility of changed numbers of organisms by medication have been known as representative problem to diagnose HP infection correctly in bleeding peptic ulcer. In our designed two-times test (first day and seventh day), intra-gastric blood, clinically emergent state and invasiveness of the test itself are suspected as limiting factors at first day; unavoidable medicine, including acid suppressive agent, antacid and antihemorrhagic drug, are suspected as limiting factors at seventh day.

There are few published studies that compare the sensitivity of the invasive and noninvasive diagnostic test. It is important to determine the best diagnostic method of HP infection, because it is possible that invasive test aggravates the ulcer bleeding in the emergent clinical state of peptic ulcer bleeding. Noninvasive tests have disputed that these are more useful than the invasive tests and more accurately reflect HP infection status^{24, 25}. High frequency of positive results in noninvasive tests (¹³C-UBT and IgG serologic studies) was detected in our bleeding peptic ulcer patient in the first day, and UBT showed relatively high sensitivity at the seventh day. Sensitivity of the histologic test and CLO test was significantly low in the first day. In bleeding patients, we could not take more than four biopsy samples. Although more numbers of biopsies in extended site are expected to increase the result of sensitivity, we could not expand the design to take more biopsy samples in bleeding patients who were clinically unstable, in fact.

Since almost results of diagnostic tests exceed 97% of positive predictive value in peptic ulcer disease, repetitive tests are considered unnecessary in a patient who has one of the positive parameters for HP²². However, the prevalence rate of HP infection in patients with bleeding peptic ulcers has been reported to be lower than the rate in patients with nonbleeding ulcers in several studies, and our positive results of 68.8% CLO test and

75% of histologic test are low like the results of those studies¹⁹⁻²¹. If we have to select one diagnostic test to detect HP infection in patients with bleeding peptic ulcers, we make important decision about which test is preferred to represent the correct state of HP infection in bleeding peptic ulcers. There have been known factors that indicate false negative result of each diagnostic test and these include the bleeding and medication of antibiotics, H₂-receptor antagonist or proton pump inhibitors, as well as limitation of each test itself.

Although UBT is a good diagnostic noninvasive test, the factor related to false negative results is not discussed in patients with bleeding peptic ulcers. Cut-off value and gastric emptying time are main factors that decide correct diagnostic yield²⁶⁻³⁰. Intra-gastric blood and 7 days medication and gastric motility are suspected of false negative factors in the clinical setting of bleeding peptic ulcers. We may consider intra-gastric blood and changed gastric emptying time related to an unstable clinical state, and these can affect hydrolysis of labeled urea by urease producing HP, in contrast to unavoidable medication of H₂ receptor blocker which can decrease the amount of urease itself. In our study, 100% positive result of UBT in the first day represents that intra-gastric blood and gastric motility of unstable clinical state are not a factor to change results, and 90.6% of 7 days can make us suspect the effect of medication.

CLO and histologic studies could not completely detect HP infection in two-times tests also. This means that these are not good diagnostic tests in patients with bleeding peptic ulcers.

Serological testing has been well-known for easy performance and high positive result, but it also has limitations because interpretation of its results is difficult to differentiate past infection in countries with a high HP prevalence rate. Therefore, it is usually used in a limited setting of follow-up studies after HP treatment.

In conclusion, first-day histologic and CLO test are an inadequate method in detecting HP infection in patients with bleeding peptic ulcers. 7-day histologic, CLO test and UBT have a low sensitivity. Intra-gastric blood at first day and anti-ulcer medications during 7-days are suspected as risk factors of decreased sensitivity. First-day UBT can be a standard test to diagnose HP infection in patients with bleeding peptic ulcers.

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