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# The effect of *Helicobacter pylori* eradication in patients with functional dyspepsia: Assessment of different diagnostic tests

*Helikobakter pilori* eradikasyonu ve fonksiyonel dispepsi

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***Background/Aims:*** *Helicobacter pylori infection, is seen in more than 80% of adult population in Turkey. The aims of this study were 1) to evaluate the importance of the diagnostic tests 2) to investigate the relationship between Hp infection and functional dyspepsia.* ***Methods:*** *A total 75 patients with functional-dyspepsia were involved into the study. Hp infection was diagnosed by histopathological examination. CLO, cytology, culture, stool antigen and breath test. Symptom score using ROME II criteria was also evaluated to all patients. All patients were taken ranitidine-bismuth-citrate (400mg bid I day), clarithromycin (500mg bid I day) and amoxicillin (lOOOmg bid I day) for 14 days. All tests and symptom score analyses were re-applied at month land 6.* ***Results:*** *The eradication rate was 95.9%. The baseline specifity of breath test, CLO, cytology, culture and stool antigen were 87.3%, 95.4%, 95.4% 94.5% and 86.4%, respectively. The sensitivity of such tests at first month after stopping the treatment were 86.1%, 100%, 100%, 100%, 84.7%, respectively, and were 91.6%, 100%, 100%, 100%, 87.5%, respectively at six months after treatment. Symptom scores were 29.6±5.4, 15.8±4.7 and 17.9±5.3 at baseline, first month and six months after treatment, respectively (p<0.001).* ***Conclusions:*** *The success of eradication may be related to use of bismuth which prevents antibiotic resistance development. Stool antigen and breath tests are less effective than invasive diagnostic-tests. The finding of improved symptomscores after eradication suggests that Hp may play a role in functional dyspepsia.*

Key words: *Helicobacter pylori,* bismuth, eradication, functional dyspepsia

***Amaç:*** *Türkiye'de erişkin populasyonda Helikobakter pilori infeksiyonu %80 den fazla oranda gözlenir. Bu çalışmanın amacı 1) tanısal testlerin önemini değerlendirmek 2) Hp infeksiyonu ile dispepsi ilişkisini araştırmaktır.* ***Method:*** *Fonksiyonel dispepsisi olan toplam 75 hasta çalışmaya dahil edildi. Hp tanısı histopatoloji ile kondu. Tüm hastalara aynı zamanda CLO, sitoloji, kültür, gaita antijeni ve nefes testi uygulandı. Tüm hastalara Roma II kriterlerine göre semptom skorlaması yapıldı. Hastalara ranitidin bizmut sitrat(400md bid9, klaritromisin(500mg bid) ve amoksisilin(1000mg bid) 14 gün boyunca uygulandı. Tüm testler ve semptom skoru 1 ve 6. aylarda tekrarlandı.* ***Sonuçlar:*** *Eradikasyon oranı %95.9 olarak bulundu. Başlangıç spesifiteleri nefes testi, CLO, sitoloji, kültür ve gaita antijeni için sırası ile %87.3, %95.4, %95.4, %94.5 ve %86.4 olarak bulundu. Aynı testlerin 1 ay sonraki sensitiviteleri 86.1%, 100%, 100%, 100%, 84.7% bulunurken, 6. ayda ise 91.6%, 100%, 100%, 100%, 87.5% şeklinde idi. Semptom skorları başlangıç, birinci ve altıncı aylarda sırası ile; 29.6±5.4, 15.8±4.7 ve 17.9±5.3 olarak bulundu(p<0.001).* ***Yorum:*** *Hp eradikasyonundaki başarı bizmutun ilaç rezistansı önleyici etkisi ile ilişkili olabilir. Histopatoloji, CLO, sitoloji ve kültür tanı koymakta etkilidir. CLO ve sitoloji sonuçları histopatoloji ile koreledir. Gaita antijeni ve nefes testi kabul edilebilir testker olmasına karşın diğer tanısal testlerden daha az etkili gibi görünmektedir. Semptom skorları tedavi ardından 6. ayda artmakla birlikte hala başlangıç değerlerinden anlamlı düşük seyretmektedir.*

Anahtar kelimeler: *Helikobakter pilori,* bizmut, eradikasyon, fonksiyonel dispepsi

## INTRODUCTION

*Helicobacter pylori (Hp)* plays a major role in the pathogenesis of gastric and duodenal ulcers. The rate of peptic ulcer disease throughout the life in *Hp* infected patients is about 3% in the USA, and 25% in Japan (1). Eradication *of Hp* lowers the recurrence rate of peptic ulcer (2). *Hp* infection also causes chronic active gastritis, gastric cancer and MALT (Mucosa Associated Lymphoid Tissue) lymphoma (3-7).

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The prevalence of *Hp* infection in adults vary in different parts of the world depending on the social and economic standards of the population (8). While the prevalence among middle aged population in developing countries is about 80%, it is only 20-50% in developed countries. The reported prevalence of *Hp* in adult population is 67.6-81.3% in Turkey (9).

Although *Hp* infection has been reported to be more frequent in patients with non-ulcer dyspepsia than control population, the role of *Hp* infection in functional dyspepsia is still controversial (10). In fact, despite *Hp* eradication, only 9% of patients with functional dyspepsia have been reported to have a regression in dyspepsia symptoms (11). Therefore it remains to be determine the role of *Hp* infection in the pathogenesis of functional dyspepsia and the effect of eradication therapy on the outcome of the disease.

Eradication of *Hp* can be achieved with different types of regimens. Success rate of generally accepted triple regimens vary between 77% and 96% (12, 13). This significant variation in eradication rate, even with similar regimens, may be related to differences in the diagnostic tests used in different clinical trials. *Hp* culture of endoscopic biopsy material has long been the gold standard of the diagnosis of *Hp* infection (14). Alternative to invasive endoscopic methods, several non-invasive methods such as breath urea test, serologic tests, and fecal antigen test can be used in the diagnosis of *Hp* infection (14).

Breath urea test relies on urease activity *of Hp* in stomach and it can detect an active *Hp* infection with a sensitivity and specifity over 90% (15). Serologic assays are cheap and easy but serology has limited value in predicting the response to therapy. In addition, in vivo sensitivity and specifity of serological tests seem to be lower than breath urea test (16). Fecal antigen test may be an option and it has 89-98% sensitivity and 90% specifity (16).This test can also be used to determine the response to treatment.

One of the aim of this study was to assess the diagnostic accuracy of non invasive tests in patients with non-ulcer dyspepsia. We also aimed to determine whether there is a relationship between *Hp* infection and dyspeptic symptoms in patients without peptic ulcer disease.

## MATERIALS AND METHODS

**Patients:** This prospective study included a total of 75 consecutive patients with *Hp* associated functional dyspepsia who were diagnosed at endoscopy unit of Gastroenterology Department of Ankara University between June 02 and September 03. The diagnosis of functional dyspepsia was based on Rome II criteria (Rome II: The Functional gastrointestinal Disorders, Second Edition, D. A. Drossman, MD University of North Carolina, USA) and all patients were carefully investigated for the following exclusion criteria after endoscopic diagnosis: presence of duodenal/gastric ulcer, former eradication therapy, antibiotic administration within last 15 days, former surgical therapy, presence of malignancy, cirrhosis and portal hypertension, esophagitis, administration of anticoagulants and presence of a systemic disease.

**Diagnosis of *Hp* infection:** *Hp* infection was diagnosed by histopathological examination of prepyloric antral biopsy material obtained during endoscopy. Then CLO test (in house), *Hp* cytology, *Hp* breath test (Helicobacter Test INFAI, INFAI-Institut fur Biomedizinische Analytik), *Hp* culture (in house) and *Hp* fecal antigen (Premier *H. Pylori*, Meridian Diagnostic Inc.) tests were performed as a diagnostic panel in all of the cases.

**Treatment regimen:** All cases received Ranitidine bismuth citrate 400 mg/d, Clarithromycin 500 mg/d, and Amoxicillin 1000 mg bid for 14 days for eradication.

**Assesment of treatment success:** Endoscopic biopsy, CLO test, *Hp* cytology, culture, *Hp* breath test, and *Hp* fecal antigen tests were all repeated at 1 and 6 months of therapy. Symptom inquiries were also repeated at similar time points.

**Statistics:** The data were analyzed with SPSS for Windows version 11.0. T test, Mann-Whitney U and Chi square tests were used where appropriate. A p value less than 0.05 was considered as statistically significant.

## RESULTS

A total of seventy-five patients presenting with *Hp* positive functional dyspepsia who completed the full course of therapy were enrolled in the study. They consisted of 49 female (65.3%) and 26 male (34.6%) patients with an average age of 41.2±12.6 years (range 16-72 years). No side effects necessitating dose reduction were encountered.

*Hp* was eradicated in 72 (95.9%) patients at 1st month of therapy. All of the *Hp* negative patients at first month were still *Hp*-negative during re-evaluation visit at month (6).

At baseline, there was a statistically significant low diagnostic yield of *Hp* breath test and *Hp* fecal antigen test when compared to CLO test, *Hp* culture and *Hp* cytology ($p<0.01$) (Table D.Specifity rates of CLO test, *Hp* culture and *Hp* cytology (95.4%, 95.4% and 94.5% respectively) were higher than that of *Hp* breath test (87.3%) and *Hp* fecal antigen test (86.4%) ($p<0.01$). These three tests were also more sensitive than both *Hp* breath test and *Hp* fecal antigen test at month 1 and 6 visits ($p<0.01$) (Table 1).

**Tablo 1.** Sensitivities and specifities of diagnostic tests at baseline and follow-up visits

| | **Baseline evaluation (%)*** | **1st month reevaluation (%)**** | **6th month reevaluation** (%)** |
|---|---|---|---|
| Breath test | (66/75) 87.3# | (64/75) 86.1* | (69/75) 91.6+ |
| CLO | (72/75) 95.4 | 100 | 100 |
| Culture | (72/75) 95.4 | 100 | 100 |
| Cytology | (71/75) 94.5 | 100 | 100 |
| Fecal antigen | (65/75) 86.4# | (63/75) 84.7* | (66/75) 87.5+ |

*Specifity, **Sensitivity, #$p<0.01$ vs. CLO, culture and cytology, *$p<0.01$ vs. CLO, culture and cytology, +$p<0.01$ vs. CLO, culture and cytology

Histopathologic examination as a gold standard, revealed positive results throughout the study in all patients.

Baseline Rome II symptom scores were significantly decreased at month 1 and 6 evaluations irrespective of treatment response (patients with eradication: $p<0.01$ vs. month 1 and month 6; patients without eradication: $p<0.05$ vs. month 1 and month 6) (Table 2). Baseline symptom scores were not different in patients with and without *Hp* eradication. However, patients who eradicated *Hp* had lower scores than patients without eradication both at month 1 and 6 evaluations (15.8±4.1 vs.25.8±8.3 and 17.9+4.9 vs.27.5±6.4, respectively $p<0.001$).

## DISCUSSION

Ranitidine bismuth citrate + Clarithromycin + Amoxicillin combination was preferred in the present study since no serious side effect has been reported so far (17). The success rate *of Hp* eradication is relatively high when compared to those in most previously published series in Turkey (55-87%) (18). Some studies in which bismuth salts were used in combination reported similar success rates (19-23). Administration of bismuth salts might be the reason of high eradication rate as it can decreases the rate of development of antibiotic-resistance. Even in antibiotic-resistant cases, eradication rate can be as high as 88% with bismuth salt containing combinations (17). Another possible explanation of relatively high eradication rate may be the high patient's compliance since all our patients completed full course of therapy.

In this study, diagnostic yields of CLO test, culture and *Hp* cytology were similar. This result is in line with the previous observation of similar specifities and sensitivities of these tests (14,24). These two tests were superior to breath test and fecal antigen detection. The finding of superiority of these tests also supports previous statements of more accuracy of invasive methods over non-invasive tests (12, 23). Taking into account the cost and easiness, CLO test or cytology seems to be preferable invasive diagnostic options compared to *Hp* culture in clinical practice. However, *Hp* culture is still thought to be the gold standard in *Hp* detection in clinical trials.

Among the non-invasive tests, breath test and fecal antigen test have been found to have similar specifity and sensitivity rates. Because of the low sensitivities of these two tests, they are expected

**Tablo 2.** Symptom scores during triple therapy

| | **Baseline Evaluation** | **1st month reevaluation** | **6th month reevaluation** |
|---|---|---|---|
| Eradicated (n:72) | 29.5±5.4# | 15.8±4.1* | 17.9±4.9+ |
| Non eradicated (n:3) | 32.7±1.1 | 25.8±8.3 | 27.5±6.4 |

#$p<0.05$, *+$p<0.001$
None of the patients in whom *Hp* was eradicated had reactivation *of Hp* infection during follow-up.

to be lower diagnostic power in the assessment of treatment response. Another disadvantages of these tests is that longer time is needed to obtain results after sampling. However, in a low prevalence area, these non-invasive tests may be more suitable in population screenings.

Baseline symptom scores significantly decreased at follow up visits. This can not be solely explained with *Hp* eradication since patients without eradication had also improvements in their symptom scores. Treatment benefit in these individuals is more likely related with the use of proton pump inhibitor. However, the decrease in symptom scores during follow-up was much more remarkable in patients who eradicated *Hp.* This latter finding suggests presence of a causal relation between *Hp* infection and functional dyspepsia in accordance with many of the recent reports (11, 25, 26). In fact, *Hp* eradication therapy has been advocated in patients with functional dyspepsia (11, 25, 27). However, common symptoms of functional dyspepsia can not be attributed to *Hp* infection alone, because symptom scores were decreased even in patients without *Hp* eradication. Further well designed studies on larger number of patients are needed to clarify the exact role *of Hp* infection and the place of eradication treatment in functional dyspepsia.

In summary, bismuth salt containing regimens have high eradication rate and may have a major role in *Hp* eradication, especially in antibiotic-resistant cases. CLO test and *Hp* cytology seem to be superior diagnostic options compared to non-invasive tests and should be preferred in the assessment of treatment efficacy in clinical trials. *Hp* plays an important role in the pathogenesis of functional dyspepsia. However, eradication can not eliminate the symptoms in a subset of patients, thus, other factors also contribute the development of the disease and symptoms.

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