EK-8

T.C.
ANKARA ÜNİVERSİTESİ

BİLİMSEL ARAŞTIRMA PROJESİ
KESİN RAPORU

Proje Başlığı: Tekrarlayan karın ağrısı olan çocuklarda Helicobacter pylori enfeksiyonu tanısında dışkıda Helicobacter pylori antigen testinin değerlendirilmesi

Proje Yürütücüsünün İsmi: Prof. Dr. Aydan Kansu

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RAPOR FORMATI

Projenin Türkçe ve İngilizce Adı ve Özetleri

Tekrarlayan karın ağrısı olan çocuklarda Helicobacter pylori enfeksiyonu tanısında dışkıda Helicobacter pylori antigen testinin değerlendirilmesi

II. Amaç ve Kapsam : *Helicobacter pylori (H. pylori)* enfeksiyonu tanısında kulanılan çeşitli testler vardır.Bu çalışmada, tekrarlayan karın ağrısı olan çocuklarda *Helicobacter pylori e*nfeksiyonu tanısında ve eradikasyonun doğrulanmasında lateral flow immunoassay yöntemine dayanan hızlı dışkı antijen testinin (Rapid HpSA test LİNEAR Chemical) yararlığını araştırılması amaçlandı

III. Materyal ve Yöntem: Çalışmaya tekrarlayan karın ağrısı olup endoskopi yapılan 109 hasta alındı. Her hastaya endoskopi, ^{14}C-üre nefes testi ve Rapid HpSA test yapıldı. Histopatolojide *Helicobacter pylori* saptanan hastalar *H. pyloriyle* enfekte hasta olarak kabul edildi. *Helicobacter pyloriyle* enfekte hastalara klaritromisin - amoksisilin (15 gün) ve omeprazolden (30 gün) oluşan üçlü tedavi başlandı. Tedavi kesildikten 4-6 hafta sonra endoskopi, ^{14}C-üre nefes testi (ÜNT) ve Rapid HpSA testi tekrarlandı.

IV. Analiz ve Bulgular Hastaların ortalama yaşı 12.1 yaş (Dağılım:5-17 yaş) idi. Çalışmaya alınan 109 çocuğun 40'ı (%36.6) *H. pylori yle* enfekte idi. Rapid HpSA testin duyarlılığı (%65) ^{14} C ÜNT'inin duyarlılığına (%92.5) göre istatistiksel olarak anlamlı düşük bulundu (p=0.003). Rapid HpSA testin (%92.3) ve ^{14} C ÜNT'inin özgüllüğü (%85) arasında istatistiksel olarak fark saptanmadı. (p=0.180). Eradikasyon tedavisi sonrası Rapid HpSA testinin duyarlılığı %60, özgüllüğü %100, ^{14} C ÜNT'inin duyarlılığı ve özgüllüğü ise %100 bulundu.

V. Sonuç ve Öneriler Sonuçlarımız çocuklarda *H. pylori* enfeksiyonunun tanısında ve eradikasyonun doğrulanmasında Rapid HpSA testinin ^{14} C üre nefes testine göre daha az güvenilir olduğunu gösterdi. Çocuklarda *H. pylori* enfeksiyonunun tanısında ve eradikasyonun doğrulanmasında invaziv olmayan, ucuz, hızlı, kolay ve her yerde uygulanabilen yeni tanı yöntemlerine gereksinim vardır.

VI. Kaynaklar (Ekteki makalede verilmiştir)

VII. Ekler

a) Mali Bilanço ve Açıklamaları :

Tüketime yönelik mal ve hizmet alımları: 2. 472. 450 TL (2472.45 YTL)

Hizmet alımları: yok

Toplam gider: 2 472.450 TL (2472.45YTL)

b) Makine ve Teçhizatın Konumu ve İlerideki Kullanımına Dair Açıklamalar (BAP Demirbaş numaraları dahil): Demirbaş alımı yok.

c) Teknik ve Bilimsel Ayrıntılar (varsa Kesim III'de yer almayan analiz ayrıntıları):

d) Sunumlar (bildiriler ve teknik raporlar): Yok

e) Yayınlar (hakemli bilimsel dergiler) ve tezler: Çalışma makale haline getirilmiş

ve SCI kapsamında yer alan isimli dergiye gönderilecektir.

NOT: Projenin İngilizce adı, özeti ve makale hali ektedir.

A Rapid lateral flow stool antigen immunoassay for the diagnosis and eradication of Helicobacter pylori infection in children with recurrent abdominal pain

Background/Aim: Several diagnostic tests are used for the detection of *Helicobacter pylori* infection. Aim of this study was to evalute the usefulness of novel, rapid stool antigen test (Rapid HpSA test LİNEAR Chemical) based on lateral flow immunoassay for diagnosing and conforming H.*pylori* infection eradication in children with chronic abdominal pain (CAP).

Methods:One hundered and nine children who have undergone upper gastrointestinal endoscopy due to CAP were included in the study. ^{14}C-UBT and Rapid HpSA test were performed to all children. Patients were considered as *H.pylori* –infected when histology was positive for *H.pylori*. *H. pylori*-infected patients were offered a tripple therapy regimen that included clarithromycin and amoxicillin (15 days) plus omeprazole (30 days). Endoscopy, ^{14}C-UBT and Rapid HpSA tests were repeated 4-6 weeks after stopping the treatment.

Results: The mean age of the children was 12.1 years (range:5-17 years). Of the 109 children, 40 (36.6%) were *H.pylori*-infected. Sensitivity of Rapid HpSA and ^{14} C UBT were 65% and 92.5% (p=0.0003), specificity of Rapid HpSA and ^{14} C UBT were 92.3% and 85.5% (p=0180). Seventeen

children were evaluated after therapy. Eradication rate was 70.5%. After eradication, sensitivity of Rapid HpSA and ^{14}C UBT were 60% and 100%, specificity of Rapid HpSA and ^{14}C UBT were %100.

Conclusion: *H.pylori* was detected in 40 (36.6%) of 109 children with CAP. The Rapid HpSA test was less reliable than ^{14}C UBT for the diagnosing and confirming eradication *H .pylori* infection in children.

A RAPID LATERAL FLOW STOOL ANTIGEN IMMUNOASSAY AND ^{14}C –UREA BREATH TEST FOR THE DIAGNOSIS AND ERADICATION OF *HELICOBACTER PYLORI* INFECTION IN CHILDREN

SHORT TITLE: Rapid stool antigen test and ^{14}C urea breath test for the diagnosis of *Helicobacter pylori* infection

ABSTRACT

Background/Aim: Several diagnostic tests are used for the detection of *Helicobacter pylori* infection. Aim of this study was to evalute the usefulness of novel, rapid stool antigen test (Rapid HpSA test LİNEAR Chemical) based on lateral flow immunoassay and ^{14}C- urea breath test (UBT) for diagnosing and conforming H.*pylori* infection eradication in children.

Methods:One hundered and nine children who have undergone upper gastrointestinal endoscopy due to abdominal symptoms were included in the study. ^{14}C-UBT and Rapid HpSA test were performed to all children. Patients were defined as *H.pylori* –infected when histology was positive for *H.pylori*. *H. pylori*-infected patients were offered a tripple therapy regimen that included clarithromycin and amoxicillin (15 days) plus omeprazole (30 days). Endoscopy, ^{14}C-UBT and Rapid HpSA tests were repeated 4-6 weeks after stopping the treatment.

Results: The mean age of the children was 12.1 years (range:5-17 years). Of the 109 children, 40 (36.6%) were *H.pylori*-infected. Sensitivity of Rapid HpSA and ^{14} C UBT were 65% and 92.5% (p=0.0003), specificity of Rapid HpSA and ^{14} C UBT were 92.3% and 85.5% (p=0180). Seventeen children were evaluated after therapy. Eradication rate was 70.5%. After eradication, sensitivity of Rapid HpSA and ^{14} C UBT were 60% and 100%, specificity of Rapid HpSA and ^{14} C UBT were %100.

Conclusion: *H.pylori* was detected in 40 (36.6%) of 109 children. ^{14}C UBT was more reliable than The Rapid HpSA test for the diagnosing and confirming eradication of *H .pylori* infection in children.

Key word: Children, *Helicobacter pylori*, Immunoassay, Immunochromatography, Stool antigen test, ^{14}C urea breath test

INTRODUCTON

Several invasive and noninvasive diagnostic tests are used for the detection of *H.pylori* infection. Histological examination is the most accurate method for diagnosis of *H. Pylori* infection in children (1,2). However, the test needs an upper gastrointestinal endoscopy associated with major disadvantages such as anesthesia and discomfort. Among the non-invasive methods, serological tests cannot be applied to young children because of low sensitivity (3). Other noninvasive test, the ure breath test is based on the detection of gastric urease produced by *H. Pylori*. The test can be performed by using ^{14}C-urea or ^{13} C urea.(4,5) It is reported that the ^{13}C urea test (UBT) has excellent sensitivity and specificity in diagnosing of *H. Pylori* infection in children (6-11), but specificity decreases in very young children, and collection of exhaled air is difficult in this age group (12,13). ^{13}C –labelled urea is preferable to ^{14}C, due to non-radioactive isotope, but high cost of ^{13}C, and requirement for mass spectrometeric analysis, preclude its use in developing countries. The ^{14} C–labelled urea is better, from an analytical, practical and economic point of view (14). Its major disadvantage is radiation exposure, however, radiation exposure secondary to this test is lower than exposure from enviromental radiation over a 24 hour period (15,16). In adults, ^{14}C UBT has been proposed as a simple, fast, sensitive and reliable method for detection of H.pylori infection in clinical practise (17-20). To the best of our knowledge, there is no report on the utility of ^{14}C UBT in diagnosis and conforming eradiacition of H.pylori infection in children.

Stool antigen tests provide a noninvasive method for the detection of *H pylori.* Recently, a novel, a rapid stool antigen test (ImmunoCard STAT HpSA, Meridian Diagnostic) based on lateral flow immunoassay (LFI) was developed. This test is inexpensive, easy-to perform without specialized laboratory equipment and it provides results in only 5 minutes. These characteristics make it a potential patient test to be used easily in the

doctor's daily practice. Several studies are reported with this new test both in adults an in children, with a widely variable performance (21-28).

The Rapid HpSA test (LİNEAR Chemical, Barcelona, Spain) is a rapid 10 minutes immunoassay based on a lateral flow chromotography technique that detects *H pylori* antigens present in human stool, and no evaluative studies of its performance have yet been reported. The aim of this study was to evaulate the usefulness of Rapid HpSA test (LİNEAR Chemical) and ^{14}C UBT (Heliprobe BreathCard) for diagnosing and conforming eradication of *H.pylori* infection in children.

MATERIAL AND METHODS

Patients

We carried out a cross-sectional study in a group of children and adolescents with abdominal symptoms suggestive of *H. Pylori* infection who were prospectively recruited to the study. Children who had received antimicrobial agents, H_2 receptor blockers or proton pump inhibitors due to any reason within 6 weeks before undergoing endoscopic examination were excluded from the study. Upper gastrointestinal system endoscopy, ^{14}C-UBT and Rapid HpSA test. were performed to all children. Sample collections for the ^{14}C UBT and Rapid HpSA test were done within a few days before or after endoscopy. During endoscopy, three biopsy specimens were collected from the antrum of stomach. Histological biopsies were stained with haematoxylin and eosin plus Giemsa stains, and gastritis was scored according to the updated Sdney System (29) by a single pathologist. The pathologist who performed histological examination was blinded to the results of all other tests.

The *H. Pylori* status (reference method) was defined as positive when histology was positive. *H. Pylori*-infected patients were offered a tripple therapy regimen that included clarithromycin (15 mg/kg/day, maximum 1 g) and amoxicillin (50 mg/kg/day, maximum 2 g) for 15 days plus omeprazole (1 mg/kg/day, maximum 40 mg/day) for 30 days.

Simple questions for symptoms were asked and endoscopy, ^{14}C-UBT and Rapid HpSA tests were repeated 4-6 weeks after stopping the treatment. During these weeks patients were not allowed to take antibiotics, H_2 antagonist or proton pomp inhibitors. Patients were classified as eradicated if histology was negative.

^{14} C urea breath test

Antacids were stopped at least 24 hour before the test, sucralfate and H_2 receptor antagonists were discontinued for 1 week before the test, and proton pump inhibitors, bismuth compounds and antibiotics were stopped for 1 month beforehand. After overnight fasting, patients swallowed 37 kBq (1 μCi) of an encapsulated form of ^{14}C-urea/citric acid composition (Helicap,Noster System AB Stockholm, Sweden) with 25 ml water. Breath samples of patients were collected with a special dry cartridge system (Heliprobe BreathCard, Noster System AB Stockholm, Sweden) at 10 min. Patients exhaled gently into the cartridge mouth piece until the indicator membrane changed colour from orange to yellow. The breathcard was inserted into a special small desktop Geiger-Muller counter (Heliprobe-analyser, Noster System AB Stockholm, Sweden) and activity counted for 250 s. 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), as suggested by the producer according to the counts obtained from the cartridges.

Rapid HpSA test (LİNEAR Chemical, Barcelona, Spain)

Rapid HPSA test was performed according to the manufacturer's recommendations without knowledge of the *H.pylori* satutus by a single biologist. This test is a rapid 10-minute test, qualitative via on a lateral flow chromotography technique. The test was considered negative if only blue coloured band (control line) appeared across the white central area of the reaction strip, and positive when, in addition to the control line, a distinguishable pink-red band (test-line) also appeared across the central zone of the reaction

strip.Any line or colour appearing after 10 minutes has no diagnostic value. Tests were also considered invalid if the control band is absent.

Statistical analysis

The statistical analysis was performed using SPSS 11.5. Statistical analyses were performed x^2 test. Sensitivity specificity, positive and negative predictive values with confidence intervals, and accuracy of the rapid HpSA and ^{14}C UBT were calculated against the defined H.pylori status as reference test. Differences between ^{14}C UBT and Rapid HpSA test was analyzed by the Mc Nemar test. A p value <0.05 was regarded as statistically significant.

Ethics

The purpose of the study was explained to all parents and children and signed consent was received prior to participation. The study protocol was approved by the ethics commitee of Ankara University.

RESULTS

A total of 125 patients are enrolled in the study. Sixteen patients were subsequently excluded. Three children failed to submit a stool (one child) or breath (2 children) sample, further 13 children refused to perform endoscopy. A total of 109 patients remained in the study (n=109, 58 girls; 51 boys, mean age; 12.1±3.1 years range: 5 to 17 year; <10 years, n=25, ≥10 years, n=84). Three children had peptic ulcer on endoscopy. Antral nodularity and erythema were observed in 22 children (20.1%).

According to the predefined criteria, 40 of 109 patients (36.6%) were *H.pylori*-infected and 69 were noninfected. *H. pylori* was documented in 31 of 109 stool samples, and in 45 of 109 ^{14}C UBT test. In the *H.pylori*-infected patients, the Rapid HpSA test was positive in 26 (65%, sensitivity) and negative in 14 (35%, false negative). In the *H.pylori*-negative patients, the Rapid HpSA test was positive in 5 (7%, false positive) and negative in

64 (93%, specificity). In the *H.pylori*-infected patients, the ^{14}C UBT was positive in 37 (92.5%, sensitivity) and negative in 3 (7.5%, false negative). In the *H.pylori*-negative patients, the ^{14}C UBT was positive in 10 (14.4%, false positive) and negative in 59 (85.5%, specificity)**.** Our results suggest that the Rapid HpSA test was less sensitive than ^{14}C UBT (p=0.003), specificity of Rapid HpSA test as compared with ^{14}C UBT was not statistically different (p=0.180). The sensitivity, specificity, positive and negative predictive values, and test accuracy, according to different age gorups, are presented in **Table 1.**

Post –eradication evaluation

All the infected patients received therapy. Seventeen of 40 treated patients returned after 6 weeks for a follow-up visit and for evalution of *H. Pylori* eradication by histology, ^{14}C UBT and Rapid HpSA test. Symptoms disappeared in 10 children (58.8%). Based on the results of histology, 5 of 17 children were *H.pylori*-infected, indicating eradication rate of 70.5% after one tripple therapy course. For the Rapid HpSA test, four patients showed positive results. ^{14}C UBT was positive in 5 of 17 children. Performance for rapid HpSA test and ^{14}C UBT tests compared with histology after *H pylori* eradication therapy is shown in **Table 2.**

DISCUSSION

The use of stool antigen tests in detection of *H. Pylori* infection has recently evoked special interest. Compared to the UBT, stool tests are obviously more convenient, particularly in pediatric patients. Stool samples can be obtained from children without their active collaboration. Several commercial stool antigen tests are available: enzyme immunoassays (EIA) and rapid lateral flow stool antigen immunassay. Conventional EIAs to detect *H. Pylori* antigens in stool is cost-effective (30), but it is a laboratory procedure, justified when multiple speciemens are tested in batch. Rapid lateral flow stool antigen immunassay allows inexpensive, 5 or 10 minute testing of single stool sample and can be easly performed

without the need for costly equipment or instrumentation, also overcoming the delays of batch testing. Therefore, it is attractive for physicans who care for children.

To the best of our knowledge, this is the first prospective study comparing Rapid HpSA test, ^{14}C UBT and histology for the diagnosing and evaluation of eradication therapy of H pylori in children. Evaluative studies of rapid immunochromotographic test (ImmnoCard STAT HpSA, Meridan Diagnostic) have been reported in both adult and pediatric pupulation. ImmnoCard STAT HpSA (Meridan Diagnostic) is unique utilized commercial kit in these studies. Evidence to date in adults suggests that this kit has a very variable sensitivity and specificity, ranging from 60 to 94.5% and from 88.5 to 100%, respectively (22,24,31-37). Performance of ImmnoCard STAT HpSA (Meridan Diagnostic) in children is also variable, in some studies lower sensitivity levels have been shown, ranging from 86.2% to 88.1%, respectively (23,27), contrasting with other studies with higher sensitivity levels, ranging from 90.6% to 100%, respectively (24,26,28). Lower sensitivities and /or specificities of the stool antigen test have been reported when stools were not immediately stored at -20 ^{0}C (38,39). Although we tested fresh stool, our results demonstrate a sensitivity of 65%, lower than previous reports. Specificity was 92.3% in our study, similar to previous reports (a specificity ranging from 76% to96) (23-28).

It has been suggested that the sensitivity and specificity of *H pylori* stool antigen test can be very low in children younger than 5 years. The reason for these findings are not well known, but some factors mentioned, such as the amount of antigens eliminated in feces which can be less in small children due to low-grade bacterial colonisation (40). A lower sensitivity of the ImmunoCard STAT HpSA tests has also been reported in children younger than 5 years with 75% sensitivity, in contrast with children older than 10 years, in which sensitivity reached to 100% (27), but this has also been contradicted (23,24,26) by other reports. In our study, there were only 2 children who were below 6 years of age. Due to the small number,

we cannot draw any conclusion for the performance of the test in toddler and preschool children. However, we found similar test performance in children younger or older than 10 years.

The role of stool antigen tests in post-eradication setting is contraversial (41).The performance of ImmunoCard STAT HpSA after eradication therapy is available in only two pediatric studies (23, 24). In these studies, after eradication therapy, sensitivity of ImmunoCard STAT HpSA compared with the reference test (^{13}C UBT) was low with 75% (24) and 88% (23). In our study, histology was accepted as the reference test because it is considered to be the most objective criterition, our results showed that Rapid HpSA test has low diagnostic accuracy after eradiacation therapy as well as in diagnosis.

^{13}C UBT is currently the gold-standard non-invasive test for the detection of *H pylori* infection in children pre and post treatment, with reported sensitivities and specifities in excess of 90% when compared with invasive method for diagnosis (3,13,42-45)13C UBT requires expensive substrate and trained staff and expensive instruments such as a mass spectometer. These are not necassary for ^{14}C-labelled UBT (14,46). The only major drawback using ^{14} C-UBT is exposure to radioisotope, however, a very small amount of radioisotope is used in ^{14}C-labelled UBT, the test actually entails low radiation exposure (0.9-3μSv). In fact the dose is less than the one day of natural radiation from enviroment (15,16). It is also reported that there is no reason for restriction on performing ^{14}C UBT, even in very young children (47). To date, there is no report on the utility of ^{14}C UBT in diagnosis and conforming eradiacition of H.pylori infection in children. Our study demonstrated that compared with histology, ^{14}C UBT showed excellent performance for both diagnosis and conforming the eradication of *H. pylori* infection. Our results are consistent with the results of the ^{13}C UBT in children (13,42-46). Morover, ^{14}C UBT was found to be more reliable

than Rapid HpSA test for diagnosis and conforming eradication evaluation of *H.pylori* infection.

We conclude that the new Heliprobe ^{14}C UBT is more reliable than the Rapid HpSA test UBT for diagnosing and confirming eradication of *H .pylori* infection in children. It is simple, rapid, inexpensive, higly accurate and its radiation burden is negligible; therefore suitable for clinical practise.

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Table 1 Performance of Rapid HpSA test and ^{14}C urea berath test compared with histology in diagnosing of H. Pylori infection by age group

Group	Method	True positive (n)	False positive (n)	True negative (n)	False negative (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
All (n=109)	Rapid HpSA	26	5	64	14	65 (45.9-77.8)	92.3 (84.1-96.8)	84 (75.3-89.9)	82 (73.2-88.5)	83
	^{14}C UBT	37	10	59	3	92.5 (80.2-97.4)	85.5 (73.3-91.9)	79.3 (69.6-85.7)	95 (88.7-98.1)	88
< 10 years (n=25)	Rapid HpSA	6	2	14	3	67 (35.4-87.9)	88 (63.9-96.5)	75.4 (53.4-93.8)	82.2(61.2-938)	80
	^{14}C UBT	9	1	15	0	100 (70-100)	94 (71.6-98.8)	90 (70-97.8)	100(83.4-99.6)	96
≥ 10 years (n=84)	Rapid HpSA	20	3	50	11	65 (46.9-78.8)	94 (84.6-98.1)	87 (77.4-93.1)	82 (71.7-89.2)	83
	^{14}C UBT	28	9	44	3	90 (75.1-96.6)	83 (70.7-90.8)	76 (64.8-84.1)	94 (85.4-97.5)	86

UBT; urea breath test PPV, positive predictive value; NPV, negative predictive value

Data in parantheses represent 95 % CI

Table. 2 Performance for Rapid HpSA test and ^{14}C urea breath test tests compared with histology post H pylori eradication therapy

Group	Method	True positive (n)	False positive (n)	True negative (n)	False negative (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
All (n=17)	Rapid HpSA	3	0	12	2	60 (23.1-88.2)	100 (75.5-100)	100 (77.1-99.4)	86(59ç4-96ç9)	88
	^{14}C UBT	5	0	12	0	100 (56.5-100)	100 (755-100)	100 (77.1-99.4)	100 (77.1-99.4)	100

UBT; urea breath test PPV, positive predictive value; NPV, negative predictive value

Data in parantheses represent 95 % CI