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Original Article

Comparison between Stool Antigen Test and Urea Breath Test for Diagnosing of *Helicobacter pylori* Infection among Children in Sulaymaniyah City

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Abstract

Objectives: Due to increasing incidence of *Helicobacter pylori* infections among children, it is important to understand which diagnostic test among the noninvasive tests is more accurate, specific, and sensitive. **Methodology:** Forty-five children who underwent osophagogastroduodenoscopy by the same pediatric gastroenterologist, with Urea Breath Test (UBT) and Stool Antigen Test (SAT); their data were analyzed by retrospective study (2013–2019) to make a comparison between UBT and SAT (Specificity, Sensitivity, and Accuracy) using biopsy finding (histopathological finding) as confirmatory tool for diagnosis. Patients were selected according to their clinical presentations and inclusion criteria in this study are: (pediatric age group, have clinical presentation of *H. pylori* infection, full information in history, clinical examination, and tests). Patients with incomplete information were excluded. **Results:** Male (75.56%) more common than female (24.44%), abdominal pain (53.3%) is the major presentation followed by hematemesis (20%), UBT is more influenced by demographic characteristics than other tests, UBT has a statistical significant correlation with result of biopsy, also it is more accurate and more sensitive than SAT, but they share same positive predictive value and same specificity. **Conclusions:** UBT more preferable than SAT specially in children above 6-year-old.

Keywords: Children, *Helicobacter pylori*, osophagogastroduodenoscopy, stool antigen test, Sulaymaniyah, urea breath test

Introduction

Helicobacter pylori (*H. pylori*) infections are considered one among the most common bacterial infections of gastrointestinal system in humans; these bacteria are Gram negative, S-shaped rods which produce urease, catalase, and oxidase, that might play a role in the pathogenesis of peptic ulcer disease. The mode of transmission for *H. pylori* still not certainly known, but many epidemiological studies strongly support human-to-human transmission and fecal-oral and oral-oral routes. Infections are thought to occur early in life (during the childhood period), and school age children in developing countries are at higher risk of *H. pylori* infection. In children *H. pylori* infection can manifest with abdominal pain, heart burn, nausea and/or vomiting and less often refractory iron deficiency anemia or growth retardation.[1-4]

Urea breath test (UBT) has been used for almost many years (around 30 years) and is still the most popular and accurate noninvasive test for diagnosis of *H. pylori* infection. By the urease activity of *H. pylori*, the ^{13}C-or^{14}C-labeled urea ingested by the patient is hydrolyzed to labeled CO_2 in stomach, then labeled CO_2 is absorbed in the blood and exhaled by breathing in which labeled CO_2 can be measured. Although several factors including patient, bacteria and the test itself influence the results of UBT, the UBT is a highly accurate and reproducible test with near 95% sensitivity and specificity under standardized procedures. UBT is also useful for epidemiological studies and for assessing the efficacy of eradication therapy.[5-7]

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While stool antigen test (SAT) is the other noninvasive method with relatively good sensitivity and specificity (94% and 97%) respectively in global meta-analysis as reported by many articles, in the diagnosis of *H. pylori* infection. This method detects the presence of *H. pylori* antigen in stool samples. There are two types of SATs used for *H. pylori* detection, enzyme immunoassay (EIA), and immunochromatography assay (ICA)-based methods, using either polyclonal antibodies or monoclonal antibodies. In general, monoclonal antibody-based tests are more accurate than polyclonal antibody-based tests and EIA-based tests provide more reliable results than ICA-based tests.[8-10] The accuracy of SAT is influenced by several factors, such as antibiotic, proton pump inhibitors (PPI), N-Acetylcysteine, bowel movement, and upper gastrointestinal bleeding. Preservation of the specimen, like temperature and transport time before testing, and cut off value also have impacts on the diagnostic accuracy of SAT.[11,12]

Other recent like polymerase chain reaction (PCR) detection test using different samples including gastric biopsy, gastric juice, stool, saliva, and dental plaque. PCR has excellent diagnostic approaches for the detection of *H. pylori*. In addition, it also tracks the several genetic alterations in bacilli for understanding the drugs resistance characteristics and co-infection of pathogens in gastric disease.[6,8,10]

Meanwhile, the histopathological study considered to be the gold standard for diagnosis of *H. pylori* infection. The accuracy of result could be affected by PPI, so it is recommended to stop PPI at least 2 weeks before performing histopathological study.[6]

This study is carried out to compare the sensitivity, specificity, and accuracy of UBT and SAT using the result of histology as a standard for comparison.

Methodology

This retrospective study includes 45 children, their ages ranging from 2 to 17-year-old, all were complaining of signs and symptoms highly suggestive of *H. pylori* infection, data were collected from medical documents (from 2013 to 2019) in Pediatric Gastrointestinal Department in Dr. Jamal Ahmed Teaching Hospital for Pediatrics (age, gender, chief complain, SAT, UBT, and biopsy histopathological findings), the osophagogastroduodenoscopy (OGD) were done by the same pediatric gastroenterologist and biopsy taken from stomach and the histopathological result considered as confirmatory tool for diagnosis. The SAT was done using monoclonal EIA and UBT was done by Richen C^{13} UBT products.

Information taken from documents (of more than 6 years 2013–2019) and they were selected for investigations according to their clinical presentations at that time (such as nausea, vomiting, heartburn, and abdominal pain) and the inclusion criteria in this study are the following: Clinical presentation suspension of *H. pylori* infection, pediatric age group, valuable history information, and were sent for UBT, SAT, and OGD. Any case with incomplete information was excluded from the study. This study has approval from Ethical Committee of Faculty of Medicine, University of Sulaimani.

Regarding statistical analysis, sensitivity, specificity, and accuracy of UBT and SAT were measured in comparison to biopsy result. Statistical Package for the Social Science (SPSS), version 26 was used, and descriptive analysis used to analyze variables. *P* value considered statistically significant if less than (0.05).

Results

The demographic characteristics of the 45 patients regarding age, gender, and clinical presentation is shown in Table 1. The majority of patients were boys (75.56%). Forty percent belong age group of 6–11 years, the mean age was (7.9 ± 4.09), and the main complaint was abdominal pain (53.3%), followed by hematemesis (20%), as shown in Figure 1.

The correlation between the demographic characteristics and the SAT, UBT, and biopsy results are shown in Table 2. Both UBT and SAT were done before biopsies. The correlation of the demographic characteristics with UBT was statistically significant ($P = 0.015$).

Table 3 shows the results of SAT and UBT in relation to biopsy results. UBT was significantly associated with the biopsy results ($P = 0.006$).

The sensitivity of UBT was much higher than that of SAT 85.7% versus 35.7%, while the specificity was similar in both 100%. The accuracy of UBT 86.7% was much higher than the accuracy of SAT 40%, as shown in Table 4.

Table 1: The demographic characteristics and clinical presentations of 45 patients

Demographic and clinical presentations	*n* (%)	Total, *n* (%)
Age (years)*		
<3	6 (13.33)	45 (100)
3-5	12 (26.67)	
6-11	18 (40.0)	
12-17	9 (20.0)	
Gender		
Boys	34 (75.56)	45 (100)
Girls	11 (24.44)	
Clinical presentations		
Abdominal pain	24 (53.3)	45 (100)
Hematemesis	9 (20.0)	
Dysphagia	3 (6.6)	
Melena	3 (6.6)	
Pallor	3 (6.6)	
Vomiting	3 (6.6)	

*Ages classified to: Infants and toddlers (<3 years), preschool age children (3-5 years), primary school age children (6-11 years) and teenage or secondary school age (12-17 years)

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Table 2: Correlations between demographic characteristics and results (*urea breath test, stool antigen test* and biopsy)

Test	Result and *P*	Demographic characteristics, *n* (%)					
		Age (years)				Gender	
		<3	3-5	6-11	12-17	Boys	Girls
SAT	Positive	0 (0.0)	3 (6.6)	9 (20.0)	3 (6.6)	9 (20.0)	6 (13.3)
	Negative	6 (13.3)	9 (20.0)	9 (20.0)	6 (13.3)	25 (55.5)	5 (11.1)
	P	0.135				0.086	
UBT	Positive	3 (6.6)	12 (26.6)	15 (33.3)	6 (13.3)	30 (66.6)	6 (13.3)
	Negative	3 (6.6)	0 (0.0)	3 (6.6)	3 (6.6)	4 (8.8)	5 (11.1)
	P	0.038*				0.015*	
Biopsy	Positive	6 (13.3)	12 (26.6)	15 (33.3)	9 (20.0)	33 (73.3)	9 (20.0)
	Negative	0 (0.0)	0 (0.0)	3 (6.6)	0 (0.0)	1 (2.2)	2 (4.44)
	P	0.185				0.143	

*Statistically significant (the UBT affected by demographic characteristics more than the other tests). *SAT: Stool antigen test, UBT: Urea breath test*

Table 3: Cross-tabulation of *stool antigen test, urea breath test* and biopsy

Tests	Biopsy, *n* (%)		*P*
	Positive	Negative	
SAT			
Positive	15 (33.3)	0 (0.0)	0.540
Negative	27 (60)	3 (6.6)	
UBT			
Positive	36 (80)	0 (0.0)	0.006*
Negative	6 (13.3)	3 (6.6)	

*Statistically significant (UBT had nearly similar results to biopsy than SAT). *SAT: Stool antigen test, UBT: Urea breath test*

Table 4: Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of stool antigen test and urea breath test

Values	SAT % (CI ratio)	UBT % (CI ratio)
Sensitivity	35.7 (21.6-52.0)	85.7 (71.5-94.6)
Specificity	100 (29.2-100)	100 (29.2-100)
PPV	100 (78.2-100)	100 (90.3-100)
NPV	10 (2.1-26.5)	33.3 (7.5-70.1)
Accuracy	40	86.7

PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval

Discussion

Because of increasing in awareness of pediatricians in the last years about *H. pylori* infections among children in our locality, the suspected cases were dramatically increased, necessitating an accurate noninvasive, cheap and applicable test for diagnosis the illness properly in order to have a better outcome. There are many tests used worldwide for diagnosing *H. pylori*, and these tests can be divided into invasive and noninvasive tests. This study is an attempt to make a comparison between sensitivity, specificity and accuracy of UBT and SAT with proved cases of *H. pylori* that were already diagnosed by biopsy (which is considered as invasive definitive diagnostic test for *H. pylori*).

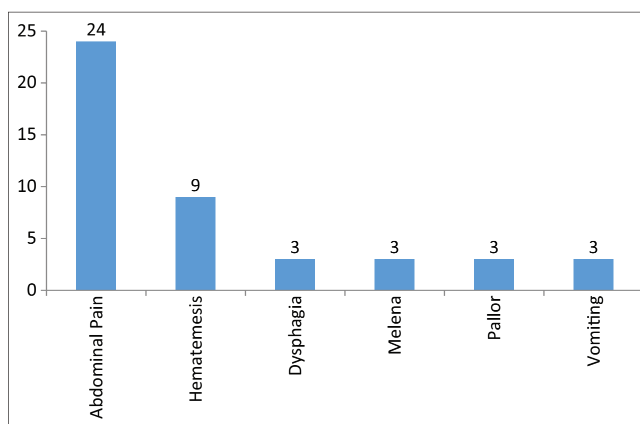

Figure 1: Frequency of patient's presentations

It is well known that biopsy remains the gold standard test for diagnosing *H. pylori*, the UBT is safe, simple, easy to perform, and noninvasive and is more sensitive and more accurate than SAT in diagnosing of *H. pylori* infection in children. The UBT is a highly accurate and reproducible test with near 95% sensitivity and specificity under standardized procedures.[5]

The majority of our patients were male 34 (75.56%), this result is quitely consistent with a study done by Castillo-Montoya *et al*. in Mexico that showing 59 (54%) were male and 51 (46%) female, and a study by Ertem *et al*. in Istanbul Turkey, 169 (51.7%) were boys and 158 (48.3%) were girls, while a study in Kurdistan/Duhok by Yahya, female (53%) were quite more than males (47%), the same result in study by Saeed in Sulaimni the male were less than female (46.9%), (53.1%), respectively,[13-16] these differences could be related to the sample sizes and methods used for collections of these samples and in order to have an accurate estimation whether male or female more liable to develop *H. pylori* we need more further studies containing large samples and for longer durations because our result may be due to relatively small sample size.

It is worthy to mention that majority of cases belong to the age group of 6–11-year-old (40%), while only (13.3%) were below 3-year-old, and this may be due to difficulty of

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diagnosing cases with *H. pylori* below this age group. The mean of ages in general is (7.9 ± 4.09), a similar result found by Ceylan *et al*. in Turkey (42.18%) between 6 and 10 years and (10.18%) below 5-year-old respectively, another study in Kampala by Hestvik *et al*. they have this result (54.8%) in the age group of 6–9-year-old.[17,18] Meanwhile a study in Erbil by Al-Mashhadany he has only (7%) from 1 to 11-year-old, but this study including all age groups and this percent consider quite common after (16%) in age group from 11 to 20-year-old,[19] the possible reason behind increasing frequency of infection above toddler age group may be related to the difficulty in taking an accurate history from toddlers and difficulty in performing some test like UBT in this age group, another possible reason could be related to breast feeding during the first 2 years of life which is considered to be protective against all types of gastrointestinal infections, in addition to other possible factors like neglecting the measures for food decontamination for children above 3 years old by parents or caregivers.

Twenty-four patients (53.3%) presented with abdominal pain, and 9 (20%) with hematemesis, while dysphagia, melena, vomiting, and pallor 3 (6.6%) for each. Most of studies about *H. pylori* sharing similar results about the abdominal pain as major symptoms in *H. pylori* infection in many reports such as (75%) in Alimohammadi *et al*., (54%) in Harris P *et al*., (76.2%) in Galal *et al*., and (63%) in Galal *et al*.[20-23] Although abdominal pain is subjective symptoms and difficult to be obtained in children particularly below 3-year-old, most of patients whether in pediatric age or adult their main complaint was abdominal pain with other signs and symptoms, and this fact mentioned in most of the text books.[1] Meanwhile other symptoms and signs may be the only presentation or together with others in some patients, like hematemesis which present in (20%) of our patients but in a study in Lebanon by Al-Kirdy *et al*. was (2.8%) only.[24] The possibility of hematemesis may increase in patients with bleeding disorders and this finding was evident in the study of Kim *et al*.[25] However, another study by Ankouane *et al.* have a result similar to our study with a percentage equal to (23.5%) among patients with associated peptic ulcer.[26]

Forty-two (93.3%) from 45 patients with clinical presentations suggestive of *H. pylori* infection have positive results in biopsy, 36 (80%) in UBT and only 15 (33.3%) in SAT respectively. Biopsy and histopathological study considered as the cornerstone for diagnosis of *H. pylori* infection. A study in Romania by Domsa *et al*. reinforces the fact that invasive methods, such as (endoscopy with biopsy) should remain the (criterion standard) for diagnosing *H. pylori* infection in children.[27]

In the current study, UBT had a statistical significant result with some demographic characters of patients in contrary to SAT and biopsy ($P = 0.038$ in UBT, it is more accurate if the age of patient above 3-year-old) and ($P = 0.015$ with gender, which shows more positive test with male gender), a similar result to a study by Kindermann *et al*. which proved that age is negatively correlated with the positive UBT ($P < 0.001$), a similar result was found by Zevit *et al*.[28,29] Regarding gender differences a study for adult patients in Israel by Eisdorfer *et al*. proved quantitative differences between men and women, also they found that environmental or host-related factors might affect quantitative value of UBT.[30]

In comparison of the positive results of UBT and SAT with the results of histopathological studies by biopsies, we can notice a clear significant statistical association between UBT and biopsy in general ($P = 0.006$) in opposite to SAT ($P = 0.540$), and as biopsy consider the most accurate test for diagnosis, so UBT is relatively more accurate than SAT, our result is consistent with Manes *et al*. study, Kato *et al*., and Jenson H.,[31-33] but these studies still recommending SAT as a quite sensitive noninvasive test for diagnosing *H. pylori* because it is noninvasive, cheap, applicable and can be performed in all ages. A recent study in 2017 by Syrjänen *et al*. recommend the use of Panel of serum biomarker (GastroPanel) for limitation both the false negative and false positive tests by both SAT and UBT.[34] There are other studies which classify the accuracy of diagnosing tests for *H. pylori* like in a study of Khalifehgholi *et al*. in Tehran which put the accuracies of tests in this way (Rapid urease test > PCR > Histology > SAT > Serology) and these results according to their finding which could require further estimation for the accuracy.[35]

In order to identify which test is more accurate (whether SAT or UBT) we calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the accuracy, in the current study results, both have same specificity and PPV while sensitivity, NPV and accuracy were more in UBT. These finding are in agreement with a study by El-Shabrawi *et al*. which recommend UBT as more affordable, simpler to perform and more tolerable with accuracy about (91.7%).[36] Another study evaluating a SAT in asymptomatic children by Saijuddin *et al*. reach to a conclusion that sensitivity and specificity of SAT in asymptomatic children with *H. pylori* infection is lower than other diagnostic tests.[37] Meanwhile an article review by Yang reveal a clear differences between children and adult in diagnosing *H. pylori* and recommend a noninvasive tests in diagnosing *H. pylori* in children due to excellent diagnostic accuracy before and after *H. pylori* eradication therapy. As children younger than 6 years tend to have high false-positive rates in applying the UBT because of difficulty in performing this test in younger children, so SAT is quietly consider as suitable test for diagnosis in this age group in spite of its sensitivity and specificity, but biopsy remains the gold standard for diagnosis in all age groups.[38]

An updated information about UBT by Sankararaman and Moosavi mentioning that UBT is the most accurate testing among the noninvasive tests, while SAT is cheaper but slightly less accurate than UBT and need stool collection which may be difficult for parents or may be not performed by some patients. UBT is useful for both the initial diagnosis of (test-and-treat

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strategy) and also in the evaluation of posttreatment status. However, serological testing may be useful for epidemiological studies and for screening larger populations in places with a higher prevalence rate. Antigen-specific serological tests in whole blood, saliva are not recommended due to their lower predictive values.[39]

Conclusions

UBT is preferred over SAT specially in children more than 6 years of age as it is more reliable and noninvasive test and quite dependable in diagnosing *H. pylori* infection in children, but in some occasions, SAT is consider useful when there is a difficulty in performing UBT or when it is not available, meanwhile biopsy remain superior.

Recommendations

Depending mostly on UBT if choosing the noninvasive method for diagnosis, and if possible on both tests to decrease the possibility of false-negative and false-positive results, and if the results still confusing the solution will be by biopsy test. It is recommended to open the gate for further evaluation of *H. pylori* infections in children by encouraging more studies in different part of Iraq that including larger samples in order to have valuable data for better estimation and better outcome.

Limitations

Small sample size, lack of data for many patients, only one pediatric gastroenterologist who perform the OGD, and lack of some facilities in government hospital (like some laboratory tests).

Ethical Issues

The Ethics Committee of Sulaimani University/School of Medicine approved the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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