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The Comparison of The Clinical Symptoms of Thypoid Fever in Adult Patients (Tubex vs Widal) in Banda Aceh, Aceh Province, Indonesia

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ABSTRACT

Introduction: Salmonella typhi bacteria infects humans through food or water contaminated by feces or urine of the patients or asymptomatic career of typhoid fever. Currently the Tubex and Widal test are the standard test to establish a definitive diagnosis for typhoid fever in Aceh. Unfortunatelly little known the differences of the sensitivity and specificity of those two diagnostic tests in the relation to clinical symptoms in adult patients with typhoid fever in dr. Zainoel Abidin General Hospital (RSU.DZA) Banda Aceh.

Objectives: To determine the differences in sensitivity and specificity between Tubex and Widal test in adult patients with typhoid fever and its relation to clinical symptoms in RSU.DZA.

Methods: We condacted an descriptive analytic with a cross-sectional design. The subjects were 75 patients aged over 18 years. Data collected from the medical records (MR) since January to December 2013. Inclusion creteria were fever ($>38^0$C) between 5-21 days, or suspected typhoid fever, and diagnosed when admitted to hospital. All the patients were test with both diagnostic tools (Tubex and Widal).

Results: Overall, from 75 sampels were tested. Most of the samples ages between 19-28 years old (45%) with male 69%. The sensitivity and specificity of the Tubex test was 84.21 % and 69.64 % respectively. 48.48 % positive predictive value (PPV) and negative predictive value (NPV) were 92.86 %. Fever was found in the whole subject of the research and became the main symptom of the patients when admitted to hospital, followed by headache, abdominal pain, nausea, vomiting and chills.

Conclution: No differences of the Tubex and Widal test related to clinical symptoms and fever ($>38^0$C) was dominant funded.

Keywords: Salmonella typhi, comparison, Tubex test, Widal test, RSU.DZA, Banda Aceh.

INTISASRI

Pendahuluan: Penyakit infeksi Salmonella thyposa dapat ditularkan dari makanan dan air yang terkontaminasi dari faeses dan urine pasien yang terinfeksi Thypoid namun tidak menunjukkan gejala klinis. Saat ini penentuan diagnosis pada pasien thypoid menggunakan uji widal dan Tubex. Perbedaan nilai sensitifitas dan spesifisitas dari alat uji yang digunakan di Rumah Sakit Umum Dr. Zainoel Abidin (RSU. DZA) dalam menentukan diagnosis thypoid yang dihubungkan dengan gejala klinis pada pasien dewasa penting untuk dilakukan.

Tujuan: Tujuan penelitian membandingkan nilai sensitifitas dan spesifisitas antara dua alat uji demam thypoid (Tubex vs Widal) yang dihubungkan dengan gejala klinis di RSU. DZA. Banda Aceh.

Metode: Penelitian ini menggunakan metode deskriptif analitik dengan desain *cross-sectional*. Total sebanyak 75 pasien terlibat sebagai responden penelitian berdasarkan data *medical record* (MR) dari 01 januari-31 desember 2013. Pemilihan sampel berdasarkan usia lebih 18 tahun, adanya riwayat demam 5-21 hari, dan terdiagnosa suspek demam thypoid.

Hasil: Nilai sensitivity dan spesifisitas dari alat uji Tubex= 84.21% dan 69.64%, dengan nilai positive predictive value 48.48% dan nilai negative predictive value= 92.86%.

Simpulan: Tidak ada perbedaan pada nilai sensitivitas dan spesifisitas dari kedua alat uji (Tubex vs Widal test) berdasarkan gejala klinis. Demam, nyeri kepala dan mual muntah merupakan gejala klinisa terbesar ditemukan.

Kata kunci: Salmonella thyposa, perbandingan, tubex test, widal test, RSU.DZA, Banda Aceh.

INTRODUCTION

World Health Organization (WHO) said there are 21.7 million cases of typhoid fever in the world in 2000 with the 216.510 people died. Ninety percent of the cases of typhoid fever occurred in developing countries[1-3]. The Number of incidence of typhoid fever in Indonesia is about 900,000 cases per year and causes approximately 20,000 deaths. The World Health Organization also reported the incidence of typhoid fever in Indonesia with the result of blood cultur positive reached 1,026 cases per 100,000 population yearly. Ninety-one percent of patients aged 3-19 years old[1,3-5]. The incidence number of typhoid fever in Aceh is 2,362 cases in 2011.[4] TUBEX and Widal tests are used as supporting tests for the patients suspected typhoid fever. The study by Olsen, et al[12] said the difference between Tubex and Widal tests: the sensitivity of Tubex 78% and Widal 64%; The specificity of Tubex 94% and Widal 76%. The study by Lim[13] said the sensitivity and specificity of Tubex is higher; 94% and can reach from 80,4-93%[12,13].

The differences of the diagnostic tests between Tubex and Widal based on the sensitivity and specificity of those two diagnostic tests that encourage researcher to conduct this comparative research on diagnostic test between Tubex and Widal to the clinical symptoms in adult patients with typhoid fever in RSUDZA Banda Aceh. The hypothesis of this study is that the Tubex test is more sensitive and more specific than Widal test depend on the clinical symptoms of typhoid fever in RSUDZA.

MATERIALS AND METHODS

The samples of this research were patients aged over 18 years old with fever between 5 to 21 days or diagnosed suspected typhoid fever in Zainoel Abidin Hospital Banda Aceh. The subjects of this research must fulfill the inclusion and exclusion criteria. These diagnostic tests used to determine the sensitivity, specificity, positive predictive value and negative predictive value[1]. This research was conducted in the Medical Record Installation, inpatient and outpatient treatment in dr. Zainoel Abidin Hospital (RSUZA) Banda Aceh from January 2013 to Desember 2013, the entire population of this research is the medical records of patients diagnosed with Typhoid Fever. The minimum number of the samples is 71 patients determinated by randomization techniques. The data taken was

secondary data obtained after administration process and the permission from the Faculty of Medicine and General Hospital dr. Zainoel Abidin Banda Aceh. The data obtained by first noting the medical record of the typhoid fever patients in January 1st to December 31st 2013.

The inclusion criteria in this study are: fever ranges between 5-21 days, patients that suspected typhoid fever, the clinical diagnosis is made by physician depend on clinical symptoms; fever, chills, headache, nausea/vomiting, cough, obstipation, diarrhea, impaired consciousness, myalgia, epistaxis, abdominal pain, seizures and patients admitted with a diagnosis other than typhoid fever previously (suspected) then the diagnosis changed into typhoid fever during treatment. The exclusion criteria in this study is: a risk factor of HIV, in immunosuppresan therapy or in immunocompromised conditions. The samples of this research was selected based on the inclusion and exclusion criteria.

We used medical records and the results of laboratory tests from the whole patiens. Data analysis were used by standard protocols from tebux and widal test guidelines. To calculate the sensitivity, specificity, positive predictive value and negative predictive value by using univariate analysis to show the distribution of frequency of each variable.

RESULTS AND DISCUSSION

The subject of this research collected from the medical records from January 1st to December 31st 2013 that conducted during March 2014. During that 1-year period we found 75 patients both men and women as the sample with symptoms of fever between 5-21 days, that fulfill the inclusion and exclusion criteria.

The characteristics of subjects of this study according to age, sex and clinical symptoms include: fever, chills, headache, nausea, vomiting, cough, obstipation, diarrhea, loss of consciousness, myalgia, epistaxis, and abdominal pain.

Typhoid fever patients classified by age: there were 34 patients (45%) in 19-28 years old group, in 29-38 years old group there were 25 patients (33%), in 39-48 years old group there were 10 patients (13%), in 49-58 years old group there were 2 patients (2.6%) and ≥ 59 years old there were 4 patients (5.3%). The highest number of patients with both tubex and widal test result positive is in 19-28 years old group (6 patients/37,5%). The highest number of patient with negative tubex test result but positive widal test result is 2 patients in 19-28 years old group (2 patients/66,7%). The highest number of patient with both tubex and widal test results negative is in 19-28 years old group (17 patients/50%). The highest number of patients with positive tubex test result but negative widal test result is in 29-38 years old group (7 patients/41.2%). The number of male patients in this study is 52 people (70%) while female patients is 23 people (30%).

Fever was found in all of the subjects (75 patients/100%) and became the main symptom when entering the hospital, followed by headache 46 patients (61.33%), abdominal pain 42 patients (56%), nausea and vomiting in 40 patients (53.33%) and chills 38 patients (50.67%).

Table 1.   Characteristics of The Research Subjects Classified by Age, Sex, and Clinical Symptoms

Variables	T(+),W(+)	T(+),W(-)	T(-),W(+)	T(-),W(-)	Total	%
Age (Years)						
• 19-28	6	9	2	17	34	45
• 29-38	5	7	1	12	25	33
• 39-48	1	1	0	8	10	13
• 49-58	0	0	0	2	2	3
• ≥ 59	4	0	0	0	4	5
Sex						
• Man	10	12	2	28	52	69
• Woman	6	5	1	11	23	31
Clinical Symptoms						
• Fever	16	17	3	39	75	100
• Headaches	13	9	2	22	46	61
• Abdominal pain	11	13	1	17	42	56
• Nausea vomiting	12	9	2	17	40	53
• Shivering	5	11	3	19	38	51
• Obstipation	4	5	0	11	20	27
• Myalgia	5	0	0	10	15	20
• Diarrhea	3	2	0	8	13	17
• Cough	1	4	1	6	12	16
• Awareness decreased	1	0	0	0	1	1

Remarks: T (+): Positive Tubex Test Results, W (+): Positive Widal Test Results, T (-): Negative Tubex Test Result, and W (-): negative Widal Test Results

Widal test for Salmonella typhi bacteria positive in 19 patients. Negative Widal test results obtained in 56 patients. Existing data were grouped into two major groups, namely Positive widal test group and Negative widal test group. For further analysis, it is available in Table 2.

Table 2. Number of Patients in Widal Test Group

	Widal test positive*	Widal test negative*	Total
Samples (n)	19	56	75

Remarks: * patients with fever range 5-21 days

From the results, the 16 patients included in the group of true positive, 17 patients included in the group of false positive, 3 patients included in the false negative group and 39 patients included in the group of true negative.

Table 3. Number of Patients Suspected Typhoid Fever

Variables		Widal (+)	Widal (-)	Total
Results of Tubex Test	Positive	16 (a)	17 (b)	33 (a+b)
	Negative	3 (c)	39 (d)	42 (c+d)
Total		19 (a+c)	56 (b+d)	75 (a+b+c+d)

Remarks: a: true positive, b: false positive, c: false negative, d: true negative

The Statistical test show the results as follows: sensitivity of Tubex is 84%, its specificity is 70%, its positive predictive value is 48%, and its negative predictive value is 93%.

Table 4. Diagnostic Value of TUBEX Test

Dependent Variable (%)	Calculation	Number of segments	Result (%)
Sensitivity	a / a + c	(16/(16+3))	84,21
Specificity	d / b + d	(39/(17+39))	69,64
Positive predictive value	a/ a + b	(16/(16+17))	48,48
Negative predictive value	d/ c + d	(39/(3+39))	92,86

Remark : a: true positive, b: false positive, c: false negative, d: true negative

Fever is the main symptom during hospital admission (100%). Marcial dkk[62] in Manila reported that fever is the main symptom in 76.7% of patients. Fever complained by 96.6% of patients and fever accompanied by chills complained by 46.1% patients[62]. Dimas et al in his study at the Hospital Dr. Hasan Sadikin in 2011 reported that the fever was found in all of the subjects and was the main symptom on a sample of 140 patients from 169 patients (83%) when admit to hospital, followed by loss of consciousness in 11 patients (6.7%), another symptom is diarrhea or hematokhezia (defecating bloody red color) and vomiting respectively in 6 patients (3.3%)[63]. Pegues et al. in 2005 reported that the typical symptoms of constipation and abdominal pain is only present in 23% and 46.7% patients[10]. The main clinical symptoms in the negative tubex and positive widal group (T-, W +) and positive tubex and negative widal group (T +, W-) is the same, both showed fever as the main symptom (17 patients), chills (11 patients), abdominal pain (13 patients), headache (9 patients) and nausea and vomiting (9 patients). Negative Tubex and positive widal group (T-,W+) also obtained the same highest clinical symptoms; fever (3 patients), followed by chills (3 patients), headache (2 patients), nausea and vomiting (2 patients) and abdominal pain (1 patient).

This research obtains the 39 patients showed clinical symptoms of typhoid fever but did not show positive results on serologic TUBEX and Widal test. This is caused by the difference in effective time of blood test checks between those two types serologic tests. Tubex test effectively done in the first week since symptoms appeared while effective Widal test done on the second and third week. This is because due to IgM began to form on day 5 and the titre increased to reach at day 14, last up to 3 months and then levels off until its disappear[27,28]. TUBEX is a serological test for the detection of acute typhoid fever by the detection of specific IgM antibodies to antigens of Salmonella typhi O9 lipopolisakarida[11,12,13]. Widal test is a serological test to measure the levels of antibodies that agglutinate antigens O and H. Antibodies against the O antigen usually appears on day 6-8 and last for 6 months. Antibodies against the H antigen appeared at day 10-12 after the onset of illness and persist for 12 months. So the Widal test is best done in the second and third week[7,19,32]. Incompatibility serology results with clinical symptoms was caused by the examination time that is not homogeneous, in which specific IgM antibodies begin to disappear, but antibodies against antigens O and H still showed a low titer therefore just beginning to form so that in the interpretation of the negative by Widal examination. This study shows that the diagnosis based on clinical symptoms of typhoid fever is still reliable and can be strengthened by laboratory tests as a support.

Widal test positive to Salmonella typhi bacteria was found in 19 patients (25.33%) and negative Widal test results obtained in 56 patients (74.66%) whereas in endemic areas, most of the population has antibodies against antigens O and H. Tupasi et al[35] in his research in the Philippines mentions these antibodies were detected in 55% of healthy patients with a titer of 1/62 - 1/75[35]. Kundu et al[36] mentioned on his research in India, 1/80 the levels found in 8-14% of the healthy population[36]. high levels titer can also occur in patients with a previous history of typhoid fever, rheumatoid arthritis, post-vaccination (titer H), cross-react with Salmonella and other Enterobacteria[58]. negative Widal test results can occur if the gaining serum too early, malnutrition, agamaglobulinemia, post antibiotics therapy[36]. Local research in each area is needed to determine the antibody titer in normal people so it can be determined the significant threshold considered in the area. Research in Bandung by Hoesaeni et al showed a positive limit for the titer O≥1 / 160 and the titer H≥1 / 320 with a sensitivity of 77%, specificity 92%, positive predictive value 90%, and negative predictive value of 80%[33].

This research obtains the sensitivity and specificity of Tubex is 84% and 69% respectively, positive predictive value 48%, and negative predictive value of 93%. Tubex test has a sensitivity and specificity better than the Widal test. Sensitivity and specificity of the Tubex test by Kawano et al in his study in the Philippines was 95.7% and 80.4%[46]. Research by Melisa et al. in 2012 in Bandung reported sensitivity and specificity of Tubex were 92% and 53.7% respectively[64]. Lim et al. in 1998 reported the Tubex test had a sensitivity of 91.2% and a specificity of 82.3%[12].

Positive Predictive Value (PPV) is the percentage of patients with a positive Tubex test will get disease in the future that is 48%. Negative predictive value (NPV) is the possibility that people with a negative test result does not have a condition that is equal to 93%. Research by Rachmajati in Semarang in 2011 mentioned the sensitivity of Tubex is 100%, specificity 52.6%, positive predictive value 76.9% and negative predictive value of 100%[61,65].

CONCLUSION

The sensitivity of Tubex test is quite well with the value of 84.21%. Specificity Tubex test in this research is 69.64%, positive predictive value 48.48% and negative predictive value was also quite good 92.86%. There was no association between the differences of sensitivity and specificity of the Widal and Tubex test with clinical symptoms. Fever was found in all of the study subjects and was the main symptom while hospital admission, followed by headache, abdominal pain, nausea and vomiting on trembling.

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