Original Article

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Reliability of Typhidot Rapid Immunoglobulin M and Immunoglobulin G in the Diagnosis of Typhoid Fever

K Santosh Kumar[1], M Suganya[2], B Sathyamurthi[3], Heber Anandan[4]

[1]Assistant Professor, Department of Pediatrics, Madras Medical College, Chennai, Tamil Nadu, India, [2]Assistant Professor, Department of Pediatrics, Government Kilpauk Medical College, Chennai, Tamil Nadu, India, [3]Professor, Department of Pediatrics, Government, Kilpauk Medical College, Chennai, Tamil Nadu, India, [4]Senior Clinical Scientist, Department of Clinical Research, Agarwal's Health Care Limited, Tirunelveli, Tamil Nadu India

Abstract

Background: Typhoid is a major health problem worldwide. A clinical spectrum of typhoid varies widely. It causes significant complications as well as mortality.

Aim: To evaluate the reliability of typhidot rapid immunoglobulin M (IgM) and immunoglobulin G (IgG) in the diagnosis of typhoid fever.

Materials and Methods: A descriptive analytical study was performed in 197 children from 1 to 12 years admitted to the Pediatrics Department from June 2010 to June 2012. Blood culture, typhidot rapid IgM, IgG, and Widal test were performed.

Results: The study consisted of 197 children with acute febrile illness with clinical symptomatology consistent with typhoid fever. 28 of the children had *Salmonella typhi* isolated from the blood. The yield of blood culture was 28.28%. The results of the study indicate that typhidot IgM has a sensitivity of 96.43%, specificity of 54.44%, and PPV and NPV of 25.96% and 98.92%.

Conclusion: Our study demonstrates that typhidot IgM has all the attributes of an ideal screening test.

Key words: Diagnosis, Elisa, Typhoid fever, Typhidot, Widal test

INTRODUCTION

Right since the isolation of the bacilli by Dr. Gaffkey, typhoid fever is one of those diseases were a lot is known about the pathogenesis of the disease but still it has been difficult to control the infection and prevent its life-threatening complications. Over the years, typhoid has been a major public health problem. It contributes significantly to the morbidity and mortality among children worldwide and more so in developing countries like India. The global burden of the illness is on the rise the current global incidence of the illness is estimated to be 22 million cases of typhoid fever and 200,000 deaths,[1] an additional 6 million cases of paratyphoid fever are estimated to occur annually. It has been 184 years since Dr. P. Ch. A. Louis first described typhoid illness based on the clinical expression of the disease to differentiate it from other acute febrile illness but even today typhoid fever continues to be an enigma to clinicians.[2] The incubation period of these Gram-negative bacteria is variable and depends on the infective dose. Clinical spectrum of the disease varies from mild undifferentiated fever to rapidly fatal disease depending on the antibiotic used, day of illness when antibiotic was initiated, age of the subject, prior vaccination status, virulence of the organism, host factors that include immunodeficiency states, concomitant drug intake.

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Aims and Objectives

The aim of the study is to evaluate the reliability of typhidot rapid IgM and IgG in the diagnosis of typhoid fever in pediatrics.

MATERIALS AND METHODS

The descriptive analytical study was performed in Department of Pediatrics in Kilpauk Medical College

Corresponding Author: Heber Anandan, Dr. Agarwal's Health Care Limited, No. 10, South Bypass Road, Vannarpettai, Tirunelveli - 627 003, Tamil Nadu, India. Phone: +91-9894067910. E-mail: clinicalresearch@dragarwal.com

Hospital from June 2010 to June 2012. Ethical Committee approval and consent from the parents of the children were obtained. Children from 1 to 12 years with history of fever more than 3 days duration with clinical manifestations suggestive of typhoid fever (history of fever of 3 days or more before admission plus documentation of fever (or to 38°C) in the hospital (both are essential for diagnosis) and any two of the following - headache, malaise, anorexia, relative bradycardia, constipation or diarrhoea, non-productive cough, intestinal hemorrhage or perforations, rosaceous rash, organomegaly, signs of toxemia were included in the study. Children with a history of typhoid immunization in the recent past two years, history of congenital or acquired immunodeficiency disorders, history of immune suppressive therapy in the past 1-month, Grade 4 protein energy malnutrition are excluded from the study. Blood culture, Widal test, typhidot rapid IgM and IgG were performed. Outcomes are sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios of typhidot rapid IgM and IgG in comparison with blood culture as gold standard. All the statistical analysis was performed through Openepi version 2.3.1 and SPSS for windows version 17.0 software (SPSS Inc, New York). McNemar test, Chi-square test, and Student's *t*-test were used to assess the statistical significance.

RESULTS

The study consisted of 197 children with acute febrile illness with clinical symptomatology consistent with typhoid fever. The mean age of the study population was 7.431 years. There were 101 female children and 96 male children included in the study. Of the 197 children included in the study, 98 of the children had an alternative diagnosis on further evaluation. Only 99 children had a clinical symptomatology and culture or serological evidence of typhoid fever. Blood culture has remained the gold standard for diagnosis of typhoid fever. Typhidot IgM, IgG and Widal test results are cross tabulated with results blood culture to study the sensitivity and specificity it shown statistical significant difference p <0.0001 (Tables 1-3). Diagnostic accuracy of typhidot IgM is higher than the other tests. (Table 4)

Table 1: Cross tabulation of typhidot rapid IgM versus blood culture

Typhidot rapid IgM	Blood culture		*P* value
	Positive	Negative	
Positive	27	77	<0.0001
Negative	1	92	

IgM: Immunoglobulin M

Table 2: Cross tabulation of typhidot rapid IgG versus blood culture

Typhidot rapid IgG	Blood culture		*P* value
	Positive	Negative	
Positive	1	115	<0.0001
Negative	27	54	

IgG: Immunoglobulin G

DISCUSSION

Typhoid fever continues to a major cause of mortality and morbidity in developing countries. Several factors contribute to the uncertainty of exactly identifying typhoid fever. The treatment of typhoid fever early is an essential factor in preventing the emergence of antibiotic resistance which is becoming increasingly common due to incorrect diagnostic test results and their interpretation. The advent of a rapid test for diagnosis of typhoid fever has come as a boon for clinicians and patients, but the reliability of these test in the Indian perspective and among children is still questionable. One such rapid test for diagnosis of typhoid is typhidot rapid IgM and IgG, which has undergone several multinational analysis. But its clinical utility among South India children with typhoid fever still remains unanswered. 28 the children had *Salmonella typhi* isolated from the blood. The yield of blood culture was 28.28%, which is comparable with culture positivity reported in other studies, which varies from 14.3% to 67.8%. In the majority of the studies, the culture yield was about 40%. The lower value obtained in our study could be explained by the early use of antibiotics by private practitioners, the blood culture yield is very low to satisfy the criterion of a diagnostic test, irrespective of the reasons for its low yield.

Table 3: Cross tabulation of typhidot rapid unpaired Widal versus blood culture

Unpaired Widal	Blood culture		*P* value
	Positive	Negative	
Positive	24	95	<0.0001
Negative	4	74	

Table 4: Comparison of test results with blood culture

Test	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Typhidot rapid IgM	96.43	54.44	25.96	98.92	60.41
Typhidot rapid IgG	3.57	31.95	0.8621	66.67	27.92
Unpaired Widal	85.71	43.79	20.17	94.87	49.75

PPV: Positive predictive value, NPV: Negative predictive value, IgM: Immunoglobulin M, IgG: Immunoglobulin G

Blood culture is a foolproof method for the diagnosis hence u an unpaired Widal and typhidot were validated against blood culture. The study also brought to light that blood culture was significantly affected by prior antibiotic intake. The mean duration of antibiotic therapy in those who have a negative blood culture was 2.93 days as against a mean duration of 1.5 days among those subjects with a positive blood culture; it gave a significant *P* value of 0.03. The results of the study indicate that typhidot IgM has a sensitivity of 96.43%, specificity of 54.44%, and PPV and NPV of 25.96% and 98.92%. This is comparable with the results obtained from several multinational studies (Table 7).

As indicated by Mitra *et al.*,[14] it is a possibility that the rapid diagnostic tests are more sensitive than blood culture which is taken as "gold standard." Hence, a result that appears to be a false positive test compared to a blood culture may, in fact, be a true-positive. This hypothesis requires further evaluation. Alternatively, a false-positive may be result of past infection with serotype typhi or another non-typhoidal *Salmonella.*[14] This could possibly explain the low specificity obtained by our study. Similar results were obtained the study conducted by Narayanappa *et al.*[11] The PPV and NPV for typhidot IgM were 25.96% and 98.92% which are characteristics of an ideal screening test. Further comparative analysis of typhidot IgM and Widal demonstrate that typhidot IgM fared better than unpaired Widal in sensitivity, specificity, PPV and NPV.

Criteria	Widal	Typhidot IgM
Sensitivity	85.71	96.43
Specificity	43.79	54.44
PPV	20.17	25.96
NPV	94.87	98.92

PPV: Positive predictive value, NPV: Negative predictive value

It is also inferred that typhidot IgM was not influence by demographic characteristics of the study population such as age, sex, and place of residence. The effect of prior antibiotic use and positivity in typhidot IgM was significantly affected. The children with prior antibiotic therapy during the initial phase of illness had significantly lower positivity which is expected as the organism would not have been able to initiate an immune response (Table 5). The mean day of illness on which typhidot positivity was seen 5.54 days. There is no statistical significance in the day of illness when typhidot IgM was taken and to the test result (p value 0.072). (Table 6) Previous studies support this findings that typhidot IgM becomes positive by 3-4 days of infection.[4] Typhidot IgM gave false positivity in 9 patients belonging to non-typhoidal group none were statistically significant, though it must be kept in mind while interpreting a positive typhidot IgM. The maximum cross-reactivity was seen with other serological test that detected specific IgM antibodies to other diseases. This could be partially explained by sharing of some common antigens, but further research and evaluation of these findings are warranted. Typhidot IgG yielded more variable results with lower sensitivity, specificity, NPV and high rate of false positivity.

Criteria	Results (%)
Sensitivity	3.57
Specificity	31.95
PPV	0.86
NPV	66.67

PPV: Positive predictive value, NPV: Negative predictive value

This phenomenon possibly indicates the high endemicity and prevalence of typhoid fever in our country were infected cases are not recognized because of the mild presentation of the disease.

Table 5: Cross tabulation of prior antibiotic therapy versus typhidot rapid IgM

Prior antibiotic therapy	Typhidot rapid IgM		*P* value
	Positive	Negative	
Received	1	23	<0.0001
Not received	92	81	

PPV: Positive predictive value, NPV: Negative predictive value, IgM: Immunoglobulin M

Table 6: Effect of day of illness on which typhidot rapid IgM

Day of illness when typhidot rapid IgM was taken	Typhidot rapid IgM		*P* value
	Positive	Negative	
Day 5	61	70	0.072
Day 6	33	18	
Day 7	10	5	
Day 8	1	0	

IgM: Immunoglobulin M

Table 7: Comparison of results of our study with previous studies

Study/published year	Sample size	Sensitivity (%)	Specificity (%)
Choo *et al.*, 1993[2]	109	95.0	75.0
Collantes and Velmonte, 1996[3]	169	93.0	100
Choo *et al.*, 1999[4]	134	93.15	80.6
Membrebe and Chau, 1998[5]	185	72.0	52.0
Olsen *et al.*, 2004[6]	59	79	89
Jesudason and Sivakumar, 2006[7]	563	92.3	98.8
Dutta *et al.*, 2006[8]	6697	90.0	100
Kawano *et al.*, 2006[9]	177	77.3	64.7
Begum *et al.*, 2009[10]	100	92.8	90.0
Narayanappa *et al.*, 2010[11]	105	92.6	37.5
Beig *et al.*, 2010[12]	145	90.0	100
Krishna *et al.*, 2011[13]	186	100	95.5
Our study	197	96.43	54.44

CONCLUSION

Our study demonstrates that typhidot IgM has all the attributes of an ideal screening test. It is a simple, rapid bedside test with a rapid turnover time, where results are available to the treating clinician within 20 min, with a good sensitivity to detect typhoid. It is affordable and a reliable screening test for diagnosis of typhoid fever in a resource-limited settings among subjects with is a very high index of suspicion of typhoid, when blood culture is not available or feasible.

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