

ORIGINAL ARTICLE

Evaluation of Diagnostic Accuracy of Typhidot Test Against Blood Culture in Diagnosis of Enteric Fever

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ABSTRACT

Objective: To determine the accuracy of Typhidot test against blood culture to diagnose Enteric Fever.

Design of Study: Cross-sectional study

Place and Period of study: Arif Memorial Teaching Hospital from August 2019 to Jan 2020.

Material and Method: A total number of 89 cases who were fulfilled the inclusion criteria with signs & symptoms of Enteric fever.

Results: There were 40 (44.9%) males and 49 (55.1%) females. 60 (67.4%) patients had positive Typhidot test while 69 (77.5%) showed positive blood culture. The typhidot showed sensitivity of 68.1%, specificity of 35%, PPV (Positive Predictive value) of 78.3%, NPV (Negative Predictive value) of 24.1% and diagnostic accuracy of 60.7% against culture (gold standard).

Conclusion: The study concludes that sensitivity & specificity of Typhidot test is less as compare to blood culture in diagnosing Enteric fever.

Keyword: Typhoid Test, Enteric fever, Blood culture, Typhidot Test, Diagnostic accuracy

INTRODUCTION

Typhoid is classical greek word 'typhos' which means smoke that was supposed to cause disease. Initially it was called Typhoid fever, name given by Louis in 1829 to distinguish it from Typhus fever. In 1869, 'Enteric fever' was suggested to distinguish it from the typhus fever¹.

Enteric fever is a substantial health issue in developed nations like Pakistan and a significant causes of mortality & morbidity. Typhoid fever is a very severe infection that is caused by bacterium *Salmonella Typhi*. People of all group of ages can be affected by this infection². Several factors can lead to this condition, including low socioeconomic status and poor sanitary system³.

The erratic indication of typhoid fever make this disease a big diagnostic challenge⁴. The characteristic demonstration including fever, diffuse abdominal pain, malaise, and constipation. It is a devastating infection that can evolve to delirium, bowel perforation, intestinal hemorrhage, and death within one month of inception and may lead to permanent neuropsychiatric problems in survivors⁵.

Enteric fever is endemic in developing countries like Pakistan, South Asia, India and Bangladesh⁶. Approximately 22 million cases of enteric fever and 200,000 deaths per year worldwide⁷. According to a statistics report mortality rate in 9.3/100000 patients in Pakistan⁸.

Since 1900 the most confirmatory method to diagnose the suspected typhoid fever is isolation of the causative organism and blood sample is main for culture for *Salmonella Typhi*⁹. Standard diagnostic method is the blood culture. It is positive in 60-80% of patients with typhoid if it is taken in appropriate volume according to the age groups. The yield of blood culture is 90% in 1st week, 75% in 2nd week followed by reduction to 50% by 3rd week and 25% by 4th week¹⁰. Percentage of positive for blood culture is only 30 to 40 because number of patients start antibiotics before taking blood sample for culture¹¹.

Cultures from other sites can also give positive results. The sensitivity of stool culture is approximately 60% in children. In addition, salmonella typhi is also excreted in urine in 25 to 30% cases. Punch biopsy sample of rose spots has a sensitivity of 65% even after administration of antibiotics¹⁰. Moreover, *Salmonella Typhi* is also present in gastrointestinal secretions and can be detected in rectal swab in 30% cases. A number of serological tests including the Widal and the Typhidot tests have been developed for rapid antigen and antibody detection. However,

these are not gold standard investigations and therefore, are not accepted internationally¹².

The Typhidot test identifies the presence of specific antibodies IgG and IgM in presence of specific membrane protein coated antigens¹³. Typhidot test has low sensitivity and specificity as compare to the blood culture. One local study, conducted in Baluchistan, found that out of 2964 clinically suspected patients, 550 (18.6%) patients were positive serologically¹⁴. While another Pakistani study, conducted in Taxilla, 760 suspected patients of typhoid fever were reported, in which 192 (25.26%) samples were positive for Widal and Typhidot test.¹⁵

Rationale of this research was to ruled out the most confirmatory test to diagnose and decision for appropriate management of enteric fever to avoid its complications. To determine the accuracy of typhidot for diagnosis of typhoid taking culture as gold standard, was the main objective of this study.

MATERIALS AND METHOD

Study Design: This is a cross-sectional study that was conducted in the Out-patient and in-patient Pediatric department of Arif Memorial Teaching Hospital within 6 months from 08-2019 to 01-2020. Sample size of 89 cases was estimated by using 18.6% prevalence of typhoid keeping confidence level at 95% taking sensitivity of Typhidot, 80% with $\pm 20\%$ and specificity of typhidot, 95% with $\pm 5\%$. On a standard proformas we were recorded the findings like detailed history and clinical examination of all children included in the study. Demographic information including age and hospital registration number was documented. Informed consent was taken from parents. Blood sample was taken by using disposable syringe under aseptic measures. All the samples were forward to the laboratory of the hospital for assessment of pathogen in blood sample and enteric fever. Blood samples were divided into two parts, oo one part Typhidot IgG and IgM was applied. On second part, culture was applied. Results were obtained & patients were confirmed as +ve or -ve. All procedure was noted on predesigned proforma.

Children with age group of 1-18 years both male and females having temp of 38°C or more than for 3 days along with either signs & symptoms of typhoid fever that are "anorexia-nervosa, vomiting, diarrhea, abdominal pain, constipation, severe headache, jaundice, and hepatosplenomegaly".

Patients with other causes of fever like malaria, UTI, otitis media, osteomyelitis, any abscesses and those with prior antibiotic therapy were excluded from this study. Blood culture was done in blood culture bottles and their sub-cultures were completed on

blood agar media. Typhidot test which is a qualitative anti-body test, that is performed to detect the presence of antibodies (IgM & IgG) to a 50kDa outer membrane protein. A +ve Typhidot result (IgG and IgM) was defined as "a noticeable reaction of an intensity equal to or greater than the control reaction on the commercially prepared filter paper".

Data Analysis Procedure: SPSS version 22 was used to analyze the data. The continuous variable factors like age & weight was demonstrated as mean & standard deviation (SV). The qualitative variables just like sex, typhidot test and blood culture were demonstrated as frequencies & percentages. A graph was generated to calculate sensitivity, specificity, PPV and NPV and diagnostic accuracy of typhidot. A p-value less < 0.05 was considered as significant.

RESULTS

Mean age of children were 7.47 ± 3.97 years. 40 (44.9%) males and 49 (55.1%) females. On typhidot, 60 (67.4%) patients were positive for enteric fever while on culture 69 (77.5%) patients were confirmed positive of enteric fever. The typhidot showed sensitivity of 68.1%, specificity of 35%, Positive predictive value (PPV) of 78.3%, Negative predictive value (NPV) of 24.1% and diagnostic precision of 60.7% against culture (gold standard). Table 1.

The value of Kappa statistics showed very weak relationship between culture and typhidot test.

Table 1: Accuracy of Typhidot for Screening of Enteric Fever

		Culture		Total
		Positive	Negative	
Typhidot	Positive	47	13	60
	Negative	22	7	29
Total		69	20	89

Sensitivity: 68.1%, Specificity: 35%, PPV: 78.3%, NPV: 24.1%, diagnostic accuracy: 60.7%, Kappa statistics = 0.027 (2.7%, p-value = 0.793)

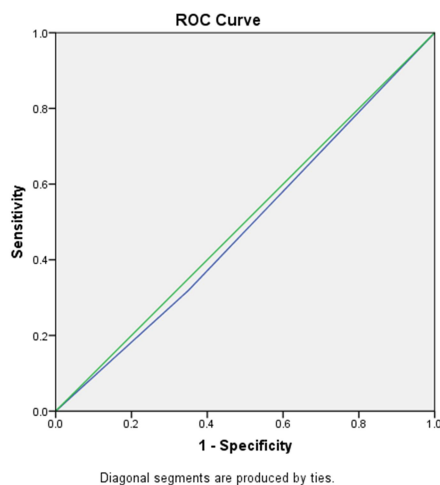


Fig 1: ROC curve with AUC

Table 2:

AUC (area under the curve)
Test Result Variable(s): typhi.dot
Area
0.484
The test result variable(s): typhi.dot has at least a tie b/w the +ve actual state group and the -ve actual state group.

DISCUSSION

In the current study, mean age of children were 3 to 7 years. This is in concordance with research from Vietnam, where rate of typhoid fever was very high in children age 5–9 years¹⁶. Whereas, another study showed mostly children of aged 5 to 18 years. Studies from South America and other countries revealed that

typhoid may present as a minor illness in pre-school children¹⁷. However, in a study conducted in South Asia indicated the rate of enteric fever in children age 2-5 years with greater risk of complications.^{18, 19}

The blood culture of clinically suspected cases was positive in 77.5 % cases in current study while in other studies blood culture positivity varied from 30.4% to 31.3% which might be attributed to prior widespread use of antibiotics⁵. Positivity of blood culture is vary in different studies.

Typhidot was positive in the 67.4% cases as compared to another study carried out in Pakistan⁶. In another study, relatively small number of cases i.e. 51.34% were positive²⁰.

Typhidot had sensitivity of 68.1% and specificity 35%. Positive predictive value (PPV) and negative predictive value (NPV) were 78.3% and 24.1% correspondingly. This is in contrary to other studies showing high sensitivity and specificity of Typhidot test. A study also showed that Typhidot-M test had specificity of 84.6%, sensitivity of 81.7%, NPV of 91.4% and PPV of 69.8%. 14 Another study carried out in India reported typhidot of having a sensitivity of 51.85% and a specificity of 98.7%, positive predictive value (PPV) of 93.33% and negative predictive value (NPV) of 85.69%, which was use to determine the diagnostic accuracy of blood culture, Typhoid IgG&IgM test, widal and polymerase chain reaction (PCR) to diagnosed the enteric fever²¹.

Our study had a limitation that the yield of blood culture is variable because the prior uses of antibiotics. In such patients the clinicians have to rely on clinical manifestations and supportive laboratory data to make the diagnosis of enteric fever. Bone marrow cultures are helpful in such situations as these may remain +ve even after 5 days of antibiotic treatment. However, bone marrow aspiration is cumbersome and is not readily accepted by the parents and patients.

CONCLUSION

Although Typhidot test is use for rapid detection of enteric fever but its sensitivity and specificity is low compared with the blood culture according to our study. Hence, we conclude that the blood culture is a gold standard method to diagnose Enteric Fever.

Conflict of interest: None

Grant support & financial disclosures: None

REFERENCES

- Ashurst JV, Truong J, Woodbury B. *Salmonella typhi*. InStatPearls [Internet] 2021 Aug 12. StatPearls Publishing.
- Andualem G, Abebe T, Kebede N, Gebre-Selassie S, Mihret A, Alemayehu H. A comparative study of Widal test with blood culture in the diagnosis of typhoid fever in febrile patients. BMC research notes. 2014 Dec;7(1):1-6.
- Ayub U, Khattak AA, Saleem A, Javed F, Siddiqui N, Hussain N, Hayat A. Incidence of typhoid fever in Islamabad, Pakistan. Am-Eurasian J Toxicol Sci. 2015;7(4):220-3.
- Parisi A, Crump JA, Glass K, Howden BP, Furuya-Kanamori L, Vilkins S, Gray DJ, Kirk MD. Health outcomes from multidrug-resistant *Salmonella* infections in high-income countries: a systematic review and meta-analysis. Foodborne Pathogens and Disease. 2018 Jul 1;15(7):428-36.
- Madeeha S, Waleed S. Case of Enteric Fever with Bicytopenia. Cureus. 2017;9(12).
- AKHTAR SJ. Determination of Baseline Antibody Titre for Widal Agglutination Test in a Specific Geographical area of Poonch, Rawalkot, Azad Kashmir.
- Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bulletin of the World Health Organization. 2004;82:346-53.
- Rasheed MK, Hasan SS, Ahmed SI. Extensively drug-resistant typhoid fever in Pakistan. The Lancet Infectious Diseases. 2019 Mar 1;19(3):242-3.
- Kundu R, Ganguly N, Ghosh TK, Yewale VN, Shah RC, Shah NK, Force IT. IAP Task Force Report: diagnosis of enteric fever in children. Indian pediatrics. 2006 Oct;43(10):875-83.
- Keddy KH, Sooka A, Letsoalo ME, Hoyland G, Chaignat CL, Morrissey AB, Crump JA. Sensitivity and specificity of typhoid fever rapid antibody tests for laboratory diagnosis at two sub-Saharan

- African sites. Bulletin of the World Health Organization. 2011;89:640-7.
11. Udayakumar S, Pushpalatha K, Sagar HN, Swathi M, Yoganand R, Sushma C. Comparative study of Typhidot-M with Widal and blood culture in diagnosis of enteric fever. Indian Journal of Child Health. 2017 Mar 28;4(1):64-7.
 12. Jabbar A, Ahmad B, Khan A. Comparative clinical utility of Widal and Typhidot in the diagnosis of typhoid fever.
 13. Khan MN, Shafee M, Hussain K, Samad A, Awan MA, Manan A, Wadood A. Typhoid fever in paediatric patients in Quetta, Balochistan, Pakistan. Pakistan journal of medical sciences. 2013 Jul;29(4):929.
 14. Bukhari N, Saleem A, Jabbar A, Khan SN, Ahmad B, Habib N, Haseeb A, Khan A, Ali MZ, Khan MA, Khan AA. Frequency of typhoid fever and its association with seasonal variations in Taxila, Pakistan. Asian Pacific journal of tropical disease. 2016 Aug 1;6(8):608-10.
 15. Naheed A, Ram PK, Brooks WA, Hossain MA, Parsons MB, Talukder KA, Mintz E, Luby S, Breiman RF. Burden of typhoid and paratyphoid fever in a densely populated urban community, Dhaka, Bangladesh. International Journal of Infectious Diseases. 2010 Sep 1;14:e93-9. .
 16. Udayakumar S, Pushpalatha K, Sagar HN, Swathi M, Yoganand R, Sushma C. Comparative study of Typhidot-M with Widal and blood culture in diagnosis of enteric fever. Indian Journal of Child Health. 2017 Mar 28;4(1):64-7.
 17. Sinha A, Sazawal S, Kumar R, Sood S, Reddaiah VP, Singh B, Rao M, Naficy A, Clemens JD, Bhan MK. Typhoid fever in children aged less than 5 years. The Lancet. 1999 Aug 28;354(9180):734-7.
 18. Ochiai RL, Acosta CJ, Danovaro-Holliday MC, Baiqing D, Bhattacharya SK, Agtini MD, Bhutta ZA, Canh DG, Ali M, Shin S, Wain J. A study of typhoid fever in five Asian countries: disease burden and implications for controls. Bulletin of the world health organization. 2008 Apr;86(4):260-8.
 19. SUBHANI A. A comparison of Typhidot test with Widal test and Blood culture for the diagnosis of Enteric Fever (Typhoid fever) in a Tertiary Care Hospital.
 20. Akhtar A, Shukla I, Khan F, Parvez A. Comparative evaluation of Blood culture, Immunochromatographic test, Widal and Polymerase chain reaction for rapid diagnosis of enteric fever. British J Med Health Res. 2016;3:39-47.