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Reliability of Typhidot-M in diagnosis of typhoid fever in children

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ABSTRACT

Background: Typhoid fever continues to be endemic and a major cause of mortality and morbidity in the developing countries. Many times, it presents a diagnostic challenge to treating physicians due to overlapping clinical features with other common causes of acute fever. A rapid and reliable laboratory test would be of great help to clinicians for early diagnosis and appropriate treatment of typhoid fever. **Aims and Objectives:** The present study was conducted to assess the reliability of Typhidot-M in diagnosis of typhoid fever. **Materials and Methods:** A total of 203 children with clinical features consistent with typhoid fever were enrolled in the study. Blood culture, Typhidot-M, and Widal test were performed. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for Typhidot-M and Widal test in comparison with blood culture as reference standard. **Results:** Out of 203 patients, 30 (14.8%) were blood culture positive. One hundred and six patients were Typhidot-M positive and 97 were negative. Typhidot-M had a sensitivity of 93.3%, specificity of 54.9%, and PPV and NPV of 26.4% and 97.9%, respectively. **Conclusion:** Typhidot-M is a sensitive test for early diagnosis of typhoid fever. However due to low specificity, positive results should be correlated with clinical picture and other possible diagnoses.

Key words: Child; Typhidot-M; Typhoid fever; Widal test

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INTRODUCTION

Typhoid fever continues to be a major public health problem in the developing countries. Global burden of the disease is estimated to be 21.6 million cases (3.6/1000 population) and 200,000 deaths/year.[1] Eight Asian countries, Bangladesh, China, India, Indonesia, Leos, Nepal, Pakistan, and Vietnam are home to approximately 80% world's typhoid fever cases.[2] The incidence is highest among young children making them the most vulnerable section of population.[3] Early diagnosis and prompt antibiotic treatment remain the key in reducing the morbidity and mortality associated with the disease along with public health measures of improvement in sanitation, safe water for drinking, health education, and vaccination.

The most common acute febrile illnesses in childhood are viral in origin and do not require antibiotic treatment. Typhoid fever, another common acute febrile illness of childhood, requires antibiotics for treatment and prevention of complications. However, due to overlapping clinical features, it cannot always be reliably differentiated from other febrile illnesses in the initial phase of illness, thereby delaying the appropriate treatment. Blood culture, the gold standard for diagnosis of typhoid fever and Widal test, the traditional test being used to diagnose typhoid fever for over a century, have their own disadvantages. Blood culture takes at least 48 h for results to be available and its sensitivity is at the most 60% in ideal conditions[4] which decreases further after the 1st week of symptoms and with prior antibiotic use.[5] Widal test is not useful for diagnosis in the 1st week of illness when it is required the most. Its

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cross-reactivity with other common pathogens in endemic areas has always been a concern.[6] A rapid diagnostic test (RDT) like Typhidot-M would be of great help to clinicians to aid the diagnosis of typhoid fever in a timely manner to start appropriate treatment.

Aims and objectives

The present study was undertaken to evaluate the reliability of Typhidot-M in the diagnosis of typhoid fever using blood culture as reference standard and to compare it with unpaired Widal test.

MATERIALS AND METHODS

This study is a hospital-based descriptive analytical study carried out in a tertiary care public hospital from South India. A written, informed consent for participation in the study was taken from parents before enrollment. The study was approved by the Institutional Ethical Committee before the commencement. A total of 203 patients were enrolled in the study. The inclusion criteria were the age group of 1–12 years; history of fever for more than 3 days duration and clinical manifestations suggestive of typhoid fever, any three or more of the following: Headache, malaise, anorexia, relative bradycardia, constipation or diarrhea, coated tongue, non-productive cough, intestinal hemorrhage or perforations, rose spots, organomegaly, and signs of toxemia. Children <1 year of age and those with a history of prior typhoid vaccination were excluded from the study. Venous blood was taken for blood culture, Widal, and Typhidot-M test from all enrolled patients. Samples for blood culture and Typhidot-M were taken immediately at the time of enrolment in the study, while sample for Widal was taken on the 7th day of fever. A 5 ml of blood by venipuncture was obtained and was incubated in brain heart infusion broth with 0.05% SPS provided by Microxpress. This was subcultured on blood agar and MacConkey agar on days 1, 2, 3, and 7. If turbidity was noted, *Salmonella* organisms were identified. The blood culture was considered negative when no growth was demonstrated after 10 days. All children were tested for Widal on the 7th day of illness irrespective of the day of admission. Typhidot-M is a dot-enzyme immunoassay (EIA), a serologic test based on the presence of specific immunoglobulin M (IgM) antibodies to a 50 kDa outer membrane protein antigen on *Salmonella typhi*. The test becomes positive as early as the 3rd–4th day of the fever. The results can be interpreted visually and available within 20 min. Typhidot-M was performed at the time of enrollment in the study. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of Typhidot-M and Widal test were determined using blood culture positivity as reference standard. Statistical analysis was done through Minitab for Windows version 15.0 software. OpenEpi version 2.3.1 was used to calculate sensitivity, specificity, PPV, and NPV.

RESULTS

In the present study, 203 children with acute febrile illness and clinical features consistent with typhoid fever were enrolled. The mean age of the study population was 7.6 years. There were 104 (51.2%) female and 99 (48.8%) male children. Out of 203 patients, 30 were blood culture positive and remaining 173 were culture negative. A total of 106 patients were Typhidot-M positive and 97 were negative. Out of 30 culture-positive patients, 28 were Typhidot-M positive and 2 were Typhidot-M negative. Out of 173 culture-negative patients, 78 were Typhidot-M positive and 95 were Typhidot-M negative. A total of 108 patients were Widal positive and 95 were negative. Out of 30 culture-positive patients, 25 were also Widal positive and five were negative. Out of 173 culture-negative patients, 83 were Widal positive and 90 were Widal negative (Tables 1 and 2). A total of 98 patients had non-typhoid final diagnosis (Table 3). Typhidot-M was false positive in 26 of these patients. For remaining 75 patients, although culture was negative, final diagnosis remained typhoid fever on clinical grounds.

DISCUSSION

Typhoid fever continues to be endemic and a major cause of mortality and morbidity in South East Asia region.[1,2] While the developed countries have achieved control over water-borne diseases through public health measures such

Table 1: Comparison of Typhidot-M and Widal test with blood culture

Blood culture	Typhidot-M (%)		Widal test (%)	
	Positive	Negative	Positive	Negative
Positive (n=30)	28 (93.3)	2 (6.6)	25 (83.3)	5 (16.6)
Negative (n=173)	78 (45.0)	95 (54.9)	83 (47.9)	90 (52.0)
Total (n=203)	106 (52.2)	97 (47.7)	108 (53.2)	95 (46.7)

Table 2: Comparison of Typhidot-M and Widal test

Parameter	Typhidot-M (95% CIs)	Widal (95% CIs)
Sensitivity	93.3 (78.6, 98.1)	83.3 (66.4, 92.6)
Specificity	54.9 (47.4, 62.1)	52.0 (44.6, 59.3)
Positive predictive value	26.4 (47.4, 62.1)	23.1 (16.2, 31.9)
Negative predictive value	97.9 (47.4, 62.1)	94.7 (88.2, 97.7)
Diagnostic accuracy	60.6 (53.7, 67.0)	56.6 (49.7, 63.2)

as safe drinking water and better sanitation, the same has not been achieved in the developing countries. Eight Asian countries, Bangladesh, China, India, Indonesia, Leos, Nepal, Pakistan, and Vietnam are home to approximately 80% world's typhoid fever cases.[2] Young children are most vulnerable.[3] Early diagnosis and institution of appropriate antibiotic therapy is the key to reduce morbidity and to prevent complications.

Blood culture, although the gold standard for diagnosis of typhoid fever, has its own limitations. Blood culture sensitivity in ideal conditions is only up to 60% in the 1st week of disease. Prior antibiotic use further reduces the diagnostic yield.[4,5] Blood culture results take at least 48 h to be available. It is much more costly and requires higher laboratory expertise. Yield of blood culture is less than satisfactory and it may not detect all true cases of typhoid fever. In resource-limited settings, facilities for blood culture may not be available at all places. Widal test, although a century old test, its diagnostic value has always been questionable. It is not useful for diagnosis in the 1st week of illness when it is required the most. High cross-reactivity with other common pathogens in endemic area makes it less reliable.[6] On the other hand, it is cheap and more readily available even in resource-limited settings.

Typhidot-M is an EIA which promises to offer many unique advantages. It is rapid, results are available within hours. It can be used in the 1st week of illness. It requires minimal operational expertise. In our study, we enrolled 203 children with acute febrile illness with clinical features consistent with typhoid fever. In our study, Typhidot-M had a sensitivity of 93.3% and specificity of 54.9%, and PPV and NPV of 26.4 % and 97.9%, respectively (Table 2). Higher NPV (97.9%) suggests that Typhidot-M is better in ruling out typhoid fever when negative, while low specificity (54.9%) could mean high false positivity. In our study, false positivity of Typhidot-M was 26.5% (Table 3). With blood culture being not fully sensitive, it is likely to be negative in some true cases of typhoid fever. With high sensitivity (93.3%), Typhidot-M promises to detect some of these true cases correctly.

Various studies have reported conflicting results and conclusions about reliability of Typhidot-M. Some have concluded that Typhidot-M is sensitive and reliable test for diagnosis of typhoid fever, while others have questioned its value (Table 4).[7-10]

In a study comprising 105 children, Narayanappa et al., found out the sensitivity and specificity of Typhidot-M to be 92.6% and 37.5%, respectively, and concluded that Typhidot-M is a sensitive and reliable test for diagnosis of typhoid fever.[7] In a study of 145 patients of all ages, Mehmood et al., reported sensitivity and specificity of

Table 3: Alternative non-typhoid diagnoses

Final diagnosis	False-positive Typhidot-M
Viral illnesses (n=55)	16
Malaria (n=17)	4
Leptospirosis (n=14)	3
Viral hepatitis (n=6)	2
Dengue (n=4)	1
Urinary tract infection (n=2)	0
Total (n=98)	26

Table 4: Sensitivity and specificity of Typhidot-M reported by various studies

Study	Sensitivity (%)	Specificity (%)
Narayanappa et al., 2010 (n=105) [7]	92.6	37.5
Krishna et al., 2011 (n=186) [8]	100	95.5
Mehmood et al., 2015 (n=145) [9]	26.7	61.5
Udaykumar et al., 2017 (n=270) [10]	81.7	84.6
This study (n=203)	93.3	54.9

Typhidot-M to be 26.7% and 61.5%, respectively.[9] Batti et al. found that out of 320 subjects of confirmed dengue infection on basis of clinical features and dengue IgM ELISA, 107 (33.4%) were also positive for *S. typhi* IgM suggesting cross-reactivity.[11]

In the latest Cochrane database systematic review (2017) which assessed various RDTs for typhoid fever, Typhidot test had average sensitivity of 84% (95% CI 73–91%) and specificity of 79% (95% CI 70–87%). The authors concluded that RDTs had moderate diagnostic accuracy and more robust evaluations of alternative RDTs for enteric fever are needed.[12]

In our study, Typhidot-M had better sensitivity, specificity, PPV, and NPV as compared to Widal test (Table 2). Various other studies have reported similar results.[10,13,14] Due to its numerous drawbacks, Widal test has been discontinued from clinical uses in developed countries.[6] It is continued to be used extensively developing countries, however, same should be discouraged. Further research is required before a more reliable rapid test can be found for early diagnosis of typhoid fever.

Limitations of the study

The blood culture yield in our study may have been affected by prior antibiotic treatment. However, this limitation is not unique to our study and similar observations have been made by authors in previous studies in the literature. If fact this is one of the drawbacks of blood culture as a diagnostic test for typhoid fever as discussed previously.

CONCLUSION

Typhidot-M is a sensitive test for early detection of typhoid fever. However, because of low specificity, positive results

should be interpreted in correlation with clinical picture and other possible diagnoses. We suggest further research before any recommendations can be made. Strengthening of public health measures to reduce disease burden is surely the way forward for the developing countries.

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REFERENCES

1. Crump JA, Luby SP and Mintz ED. The global burden of typhoid fever. Bull World Health Organ. 2004;82(5):346-353.
2. Chau TT, Campbell JI, Galindo CM, Van Minh Hoang N, Diep TS, Nga TT, et al. Antimicrobial drug resistance of *Salmonella enterica* serovar typhi in Asia and molecular mechanism of reduced susceptibility to the fluoroquinolones. Antimicrob Agents Chemother. 2007;51(12):4315-4323.
https://doi.org/10.1128/AAC.00294-07
3. Sinha A, Sazawal S, Kumar R, Sood S, Reddaiah VP, Singh B, et al. Typhoid fever in children aged less than 5 years. Lancet. 1999;354(9180):734-737.
https://doi.org/10.1016/S0140-6736(98)09001-1
4. Mogasale V, Ramani E, Mogasale VV and Park J. What proportion of *Salmonella* Typhi cases are detected by blood culture? A systematic literature review. Ann Clin Microbiol Antimicrob. 2016;15(1):32.
https://doi.org/10.1186/s12941-016-0147-z
5. Antillon M, Saad NJ, Baker S, Pollard AJ and Pitzer VE. The relationship between blood sample volume and diagnostic sensitivity of blood culture for typhoid and paratyphoid fever: A systematic review and meta-analysis. J Infect Dis. 2018;218(Suppl 4):S255-S2567.
https://doi.org/10.1093/infdis/jiy471
6. Olopoenia LA and King AL. Widal agglutination test 100 years later: Still plagued by controversy. Postgrad Med J. 2000;76(892):80-84.
https://doi.org/10.1136/pmj.76.892.80
7. Narayanappa D, Sripathi R, Jagdishkumar K and Rajani HS. Comparative study of dot enzyme immunoassay (Typhidot-M) and Widal test in the diagnosis of typhoid fever. Indian Pediatr. 2010;47(4):331-333.
https://doi.org/10.1007/s13312-010-0062-x
8. Krishna S, Desai S, Anjana VK and Paranthaaman RG. Typhidot (IgM) as a reliable and rapid diagnostic test for typhoid fever. Ann Trop Med Public Health. 2011;4(1):42.
9. Mehmood K, Sundus A, Naqvi IH, Ibrahim MF, Siddique O and Ibrahim NF. Typhidot-A blessing or a menace. Pak J Med Sci. 2015;31(2):439.
https://doi.org/10.12669/pjms.312.5934
10. Udayakumar S, Pushpalatha K, Sagar HN, Swathi M, Yoganand R and Sushma C. Comparative study of Typhidot-M with Widal and blood culture in diagnosis of enteric fever. Indian J Child Health. 2017;4(1):64-67.
https://doi.org/10.32677/IJCH.2017.v04.i01.017
11. Bhatti AB, Ali F and Satti SA. Cross-reactivity of rapid *Salmonella* Typhi IgM immunoassay in dengue fever without co-existing infection. Cureus. 2015;7(12):e396.
https://doi.org/10.7759/cureus.396
12. Wijedoru L, Mallett S and Parry CM. Rapid diagnostic tests for typhoid and paratyphoid (enteric) fever. Cochrane Database Syst Rev. 2017;5(5):CD008892.
https://doi.org/10.1002/14651858.CD008892.pub2
13. Khoharo HK. A comparative study of the typhidot (Dot-EIA) and Widal tests in blood culture positive cases of typhoid fever. Trop Doct. 2011;41(3):136-138.
https://doi.org/10.1258/td.2011.100406
14. Salama RI and Said NM. A comparative study of the Typhidot (Dot-EIA) versus Widal Test in diagnosis of typhoid fever among Egyptian patients. Open J Gastroenterol. 2019;9(6):91.
https://doi.org/10.4236/ojgas.2019.96011

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