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Typhidot IgM as a reliable and rapid diagnostic test for typhoid fever among children in a tertiary care hospital

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ABSTRACT

Background: Typhoid fever still continues to be a major public health problem in Nepal. A clinical spectrum of typhoid varies widely. It causes significant complication as well as mortality. A simple, reliable, affordable and rapid diagnostic test has been a long felt need of the clinicians to prescribe specific medication, adopt prevention of the emergence of antibiotics resistance and overall reduce the disease burden in the community.

Methods: The prospective descriptive study was performed in 125 children between 2 years to 15 years of age admitted to the Pediatrics Department from September 2017 to September 2018. Blood culture, Typhidot rapid IgM were performed. MEDCALC software was used to calculate 95% confidence interval for sensitivity, specificity, predictive value positive, predictive value negative and accuracy. Kappa test was used to determine the agreement between Typhidot IgM and blood culture methods.

Results: The study consisted of 125 children with acute febrile illness for more than 3 days with clinical symptomatology, consistent with typhoid fever. The reliability of Typhidot IgM in relation with blood culture and the study lighten that sensitivity 92.3% (95% CI: 63.9, 99.8), specificity 49.1% (95% CI: 39.5, 58.7), PPV 17.4% (95% CI: 14.2, 21.1), NPV 98.2% (95% CI: 89.2, 99.7) and accuracy 53.6% (95% CI: 44.5, 62.6). The two methods i.e. Typhoid IgM and blood culture shows significant agreement with p value 0.004.

Conclusions: The present study demonstrates that Typhidot IgM has all the attributes of an ideal screening test.

Keywords: Diagnostic, Typhidot IgM, Typhoid fever

INTRODUCTION

Typhoid fever is prolonged febrile illness caused by a systemic infection with Salmonella enteric serovar Typhi (S. Typhi). Paratyphoid is caused by closely related organisms Salmonella enteric Serovar Paratyphi A, Salmonella Schottmulleri (S. Paratyphi B), or Salmonella Hirshfeldii (S. Paratyphi C). S Paratyphi A is the only one of the Paratyphi that has been isolated in Nepal.^{1, 2}

Typhoid Fever occurs in all parts of the world where there is substandard water supply and sanitation. It has almost been eliminated from developed countries because of sewage and water treatment facilities but remains a common disease and a major cause of morbidity and mortality in the third world countries. Exposure of the individual to contaminated food or water closely correlates with the risk for enteric fever.^{3,4} Typhoid Fever was an important cause of illness and death in the overcrowded and unsanitary urban conditions of the United States and Europe in the 19th century.

World Health Organization (WHO) conservatively estimates the annual global incidence of typhoid fever at 0.3%. Typhoid Fever remains an important public health issue in many developing countries and predominates in areas with poor sanitation, which aids its transmission and persistence in the human population.⁵⁻⁷

The introduction of Chloramphenicol for the treatment of typhoid fever in 1948 transformed a severe debilitating disease into a readily treatable condition. However, emergence of plasmid mediated resistance and development serious side effect like bone marrow aplasia had pushed this drug aside. Trimethoprim-sulfamethoxazole and ampicillin were employed to counter chloramphenicol resistance in 1970, but it was also discarded because of development of plasmid mediated resistance.

In the 1980s, ceftriaxone and ciprofloxacin became the drug of choice. Although fluoroquinolones attain excellent tissue perforation, rapid therapeutic response and very low rate of Post Treatment Carriage, strains of bacteria have emerged in Asia that show resistance to them in past decades. Emergence of resistance to Chloramphenicol and other antimicrobial agents has been a major setback.

Authors now face the real hazard of re-emergence of untreatable typhoid fever. It is unfortunate that a disease that could be managed in the past with ease, safety and low cost is now posing a therapeutic challenge. The review of literature on subject reveals significant changes in clinical manifestations, course, neurological involvement and drug sensitivity pattern.⁹

METHODS

It's a hospital based prospective descriptive analytical study to evaluate the reliability of Typhidot IgM as a rapid diagnostic test for typhoid fever among children in a tertiary care hospital. Patient who met criteria ask to give informed consent and answer a brief questionnaire about clinical symptomatology, antimicrobial treatment and then proceed for further investigation i.e. Typhidot IgM, Blood culture and other relevant investigation.

Inclusion criteria

- Children between 2 years to 15 years of age with history of fever for more than 3 days before admission plus documentation of fever (100.40°F) in the hospital.
- Along with at least two of the following manifestation- anorexia, vomiting, headache, pain abdomen, constipation or diarrhea, sign of toxemia, rose spots, organomegaly from Pediatric OPD/ ER at NMCTH.
- Result from previous test (explain it what could happen).

Exclusion criteria

- Children with a history of typhoid immunization in the recent past two years
- History of immune suppressive therapy in the past 1 month
- Grade 4 protein energy malnutrition.

RESULTS

The study consisted of 125 Children with acute febrile illness along with clinical symptomatology consisted with typhoid fever between 2 years to 15 years of age admitted in Department of Pediatrics, National Medical college and teaching hospital. Of the 125 participants included in the study, 38 of the participants had an alternative diagnosis on further evaluation. Only 87 participants had a clinical symptomatology or culture or serological evidence of typhoid fever.

Table 1: Final diagnosis in Typhidot IgM and blood culture positive *Salmonella* typhi cases.

Final diagnosis	Typhidot IgM (n=69)		Blood culture (n=13)	
	Frequency	%	Frequency	%
Typhoid fever	62	89.9	13	100
Scrub typhus	4	5.8		
Malaria	2	2.9		
Gram negative septicemia	1	1.4		

Table 1 shows demonstration of final diagnosis in Typhidot IgM and Blood culture positive cases, among them 89.9% were typhoid fever in Typhidot IgM and 100% were typhoid fever with blood culture. 5.8% were scrub typhus in Typhidot IgM positive case, 2.9% were malaria in Typhidot IgM positive case, 1.4% were gram negative septicemia in Typhidot IgM positive cases.

Table 2: Final diagnosis in Typhidot IgM and blood culture negative *Salmonella* typhi cases.

Final	Typhidot IgM (n=56)		Blood culture (n=112)	
diagnosis	Frequency	%	Frequency	%
Typhoid fever	25	44.6	74	66.1
Scrub typhus	12	21.4	16	14.3
Malaria	4	7.1	6	5.4
Gram negative septicaemia	9	16.1	10	8.9
Tubercular meningitis	3	5.3	3	2.6
Pyogenic meningitis	2	3.6	2	1.8
Dengue fever	1	1.8	1	0.9
Total	56	100	112	100

Table 2 shows demonstration of final diagnosis in Typhidot IgM and Blood culture negative *Salmonella* typhi cases, among them 44.6% were typhoid fever in Typhidot IgM negative case and 66% were typhoid fever

with blood culture negative *Salmonella* typhi case which is clinically suspected cases. 21.4% were scrub typhus in Typhidot IgM negative case, 16.1% were gram negative septicemia in Typhidot IgM negative case whereas 14.3% and 8.9% were scrub typhus and gram-negative septicemia in blood culture negative *Salmonella* typhi cases.

Table 3: Diagnostic reliability of Typhidot IgM in relation blood culture.

Variable	Blood culture	;	_		
	Positive	Negative	p-value		
	(Frequency)	(Frequency)			
Typhidot IgM					
Positive	92.3% (12)	17.4% (57)	0.004		
Negative	98.2% (1)	49.1% (55)			

Table 3 represents the reliability of Typhidot IgM in relation with blood culture and the study lighten that sensitivity 92.3%, specificity 49.5%, PPV 17.4% and NPV 98.2% which is highly significant with p value 0.004.

DISCUSSION

This prospective descriptive study conducted to evaluate the reliability of Typhidot IgM as a rapid and early diagnostic test for typhoid fever among children between 2 years to 15 years of age with febrile illness more than 3 days with clinical symptomatology consistent with typhoid fever admitted in the Department of Pediatrics, National Medical College and Teaching Hospital, Birgunj (Nepal). Total of 125 Children were included in the study. In all Children, Blood culture, Typhidot IgM test and Base line investigation were done. Overall Typhidot IgM provides promising result as clinician expect it to. It displayed high sensitivity despite being rapid and easy to perform.

Regarding the prediction of the reliability of Typhidot IgM. The study result show 92.3% sensitivity. The sensitivity consistent with Sherwal BL et al (92%), another study done by Mary V et al, show congruent result (92.3%), Study done by Beig et al (90%) is consistent with present study. 10,11 However, in contrast study reported by Bhutta et al, reveals that 70% sensitivity of Typhidot IgM.¹² High level of sensitivity of Typhidot IgM show in present study because it show 12 positive result among 13 culture confirmed cases and 1 case out of 13 show negative result, was 4 years old child presented with 7 day of fever, False negative probably due to failure of the test to detect the antibodies or perhaps the antibodies didn't reach into the circulation at detectable level in the patient. As indicated by Mitra et al, it is a possibility that the rapid diagnostic test are more sensitive than blood culture which is taken as "gold standard."13 Hence, a result that appears to be a false positive test compared to a blood culture may, in fact, be a true positive.

The study show specificity of Typhidot IgM were 49.1%. The result congruent with the study done by Membrebe and Chua (52%), Mehmood K et al (61.5%). 14.15 In contrast study done by Begum Z et al, shows 90%. 16 The study represent low specificity is due to cross reaction between the OMP antigen of *Salmonella* typhi with *Serotype* typhi or another non-typhoidal *Salmonella*. Typhidot IgM gave false positivity in 7 participants belonging to non-typhoidal group. So, it must be kept in mind while interpreting a positive Typhidot IgM.

Typhidot IgM show PPV 17.4% and NPV 98.2%. The result congruent with study conducted by Narayanappa et al in which PPV and NPV for Typhidot IgM were 25.96% and 98.92%. ¹⁷ In contrast study conducted by Krishna S et al 89.2% PPV. ¹⁸ In present study low PPV is due to low sensitivity of blood culture. The high level of sensitivity and NPV of the Typhidot IgM suggested that Typhidot IgM would be useful in areas of high endemicity. The study lighted on diagnostic reliability of Typhidot IgM with blood culture show statistically significant with p value 0.004, in congruent with the result, study conducted by Dipankar De et al reveal with p value 0.001. ¹⁹

CONCLUSION

As present study demonstrates significant (p=0.004) association of Typhidot IgM to the diagnosis of typhoid fever. Typhidot IgM has all the attribute of an ideal screening test. It is simple with rapid turnover time, where results are available to the treating clinician within 20 mins, with a good sensitivity to detect typhoid fever. It is also an affordable and a reliable screening test for diagnosis of typhoid fever in resource limited setting among children with remarkably high suspicious of typhoid fever, when blood culture is not available or feasible.

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Institutional Ethics Committee

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