

A Comparative Study of Typhidot and Diazo Test In Early Detection and Diagnosis of Typhoid Fever In Children

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Introduction: Typhoid fever is an endemic disease and is a significant public health problem in developing countries where water supply and sanitation are substandard. It is one of the most common infectious diseases prevalent in India. The present study was undertaken to compare the sensitivity and specificity of the Typhidot test and Diazo test in suspected Typhoid cases. **Materials and Methods:** This is a one-year cross-sectional study conducted in Vydehi medical college among 100 children. All the children up to 15 years of age having a history of fever more than three days with symptoms and signs suggestive of Typhoid fever was selected for the study. Blood was taken for blood culture and typhidot. The urine sample was collected for the Diazo test. **Results:** The majority of the patients (50%) were in the age group of 6-10 years, with the majority of them from the middle class (46%). In the study, 26% of the cases were positive by blood culture, and 33% of the patients were positive by Typhidot M test compared to 34% by diazo test. The sensitivity and specificity of the typhidot test was 84% and 86% compared to the diazo test, which showed 73% and 79%. **Conclusion:** Typhidot assay is a rapid, easy to perform and reliable diagnostic test with high specificity and sensitivity compared to the Diazo test.

Keywords: Typhoid fever, Typhidot, Diazo test, Blood culture

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Introduction

Global estimate of Typhoid fever is 21 million cases annually, resulting in an estimated 216,000 - 600,000 deaths per year, predominantly in children of school age or younger, the majority of which is in Asia [1]. It is one of the most common infectious diseases prevalent in India. In 2014 the reported data showed 1.7 million cases and 429 deaths. Maximum cases were reported from Bihar (273,0007 cases with four deaths). Many cases were reported from Andhra Pradesh (186,446 cases and five deaths)[1]. Children are disproportionately affected by Typhoid fever, with a peak incidence between 5 to 15 years of age [2]. It is a life-threatening systemic infection caused by salmonella typhi usually transmitted through the feaco-oral route. Similar but often less severe disease, paratyphoid fever, is caused by Paratyphi A, B or C [2].

Early and prompt diagnosis of Typhoid is mandatory among children. With the increasing use of antibiotics, the clinical presentation is nonspecific and difficult to diagnose clinically. Since the clinical scenarios of common infections like Malaria, Typhoid, Leptospirosis and Scrub are very similar, it is very difficult for treating physicians to recognise Typhoid fever based on clinical features. Hence it is mandatory to have a valid diagnostic test with good sensitivity and specificity for early detection of enteric fever in children [3]. Although blood culture is the gold standard investigation, it is cumbersome and requires elaborate laboratory equipment. Sensitivity is also affected by the amount of blood obtained for culture. It is further reduced with the starting of antimicrobial therapy before confirmation of the diagnosis [4]. Recent advances in immunology have led to the discovery of rapid, reliable, easy perform the serological test with higher sensitivity and specificity. Typhidot is one such serological test available for rapid diagnosis [5]. A simple bedside test like Diazo which has served in epidemic situations in the past should also be re-evaluated for patients in rural or remote health settings. Diazo test becomes positive from day 5 of fever and remains positive till day 31 of fever. The average duration of test positivity was 6 to 16 days of fever [6]. We would like to compare the sensitivity and specificity of the Typhidot M and Diazo test with the blood culture as the gold standard in the early diagnosis of Typhoid fever.

Materials And Methods

Setting: This is a cross-sectional comparative study involving 100 children in the age group of up to 15 years with signs and symptoms of Typhoid fever after taking the approval of the ethics committee and informed consent from parents over one year in a tertiary care teaching hospital.

Inclusion criteria: Children up to the age of 15 years with a history of fever more than three days with clinical symptoms and signs suggestive of Typhoid fever.

Exclusion criteria: Fever patients with the alternative diagnosis were excluded from the study.

Method: Samples were obtained from children who had a fever for more than three days with symptoms and signs of typhoid fever after ethical clearance and parents consent. Two types of samples were collected—blood and urine. Around 4 ml of blood were collected with aseptic precaution from the children clinically suspected to have Typhoid fever. About 1-2 ml of blood was used for blood culture and incubated in the automated BacT/ALERT 3D system (BIOMERIEUX, USA) for 72 hours. The remaining blood was used for complete blood count and Typhidot test. Urine sample collected was subjected to a Diazo test using Diazo reagent, and the test results were noted.

Statistical Analysis

The statistical analysis was performed using SPSS statistical software (Version 24). The Chi-square test was used to observe statistical differences among the observed and experimental values of variables. All the differences would be considered statistically significant at p value < 0.05. Sensitivity, specificity, positive predictive value, negative predictive value, positive and negative likelihood ratios were calculated for the typhidot and diazo tests by comparing the results with the gold standard blood culture.

Results

Of the selected cases, 38% of the patients belong to the age group of 0-5 years, 50% of the cases belong to the age group of 6-10 years, and 12% of the cases belong to the age group of 11-15 years. The youngest patient was one year old, and the oldest patient was 13 years. Of the study

Group, 51% of selected cases were male, and 49% were female. The male to female ratio is 1:0.96. Among participants, 46% (46) belonged to the lower class, and 31% (31) belonged to the lower middle class. At the same time, 12% (12) and 11% (11) belonged to the middle class and upper-middle-class, respectively. None of the participants in this study belonged to the upper class.

Out of 100 children, 26 children had *S.typhi* grown in the blood culture method. Of the 100 cases in the study, 26% were positive by Blood Culture, 34% by Diazo test and 33% by Typhidot test. The p-value for the above tabulation is 0.41, which is not statistically significant. Among the typhoid cases detected by Blood culture, 34.6% were from the age group of 0-5 years, 46.2% were from 6-10 years, and 19.2% were from the age group of 11-15 years. Among the typhoid cases detected by the Diazo test, 47%, 32.3% and 20.7% were from the age group of 0-5 years, 6-10 years and 11-15 years, respectively. Among the typhoid cases detected by Typhidot, 39.4%, 39.4% and 21.2% were from 0-5 years, 6-10 years and 11-15 years, respectively. Thus the above tabulation shows that there is no statistical significance.

Of 26 blood culture-positive cases, 23 cases showed positive results, and 3 had a negative result by Typhidot test. The remaining 10 cases which were found to be positive using Typhidot were found negative with Blood culture. The p-value for the above tabulation is less than 0.0.5, which shows that it is statistically significant.

Of 26 blood culture-positive cases, 19 cases showed positive results and seven negative effects by the Diazo test. The remaining 15 cases which were found to be positive using the Diazo test were found negative with Blood culture. The p-value for the above tabulation is less than 0.0.5, which shows that it is statistically significant.

All three tests were positive in 17% of the selected cases. Blood culture and Diazo test positive, while Typhidot test negative was observed in 2% of the cases. Blood culture and Typhidot test positive, while Diazo test negative was observed in 6% of the cases. Only Blood culture positive while Diazo test and Typhidot negative were observed among 1% of the cases. Only blood culture-negative while Diazo test and Typhidot positive was observed among 3% of the cases. Only Diazo test positive and only Typhidot positive was observed in 12% and

7% of the cases, respectively. None of the three tests positive was observed in 52% of the cases.

Table 1: Results of Blood culture, Diazo test and Typhidot

Results	Blood Culture		Diazo Test		Typhidot	
	No.	%	No.	%	No.	%
Positive	26	26%	34	34%	33	33%
Negative	74	74%	66	66%	67	67%
Total	100	100%	100	100%	100	100%

Table 2: Comparison of Typhidot with blood culture

		Blood culture		Total
		Positive	Negative	
Typhidot	Positive	23	10	33
	Negative	3	64	67
Total		26	74	100

Table 3: Comparison of Diazo test with blood culture

		Blood culture		Total
		Positive	Negative	
Diazo test	Positive	19	15	34
	Negative	7	59	66
Total		26	74	100

Table 4: Positive and negative results of Blood culture, Diazo test and Typhidot test

Blood Culture	Diazo test	Typhidot	Number	Percentage
+	+	+	17	17%
+	+	-	2	2%
+	-	+	6	6%
+	-	-	1	1%
-	+	+	3	3%
-	+	-	12	12%
-	-	+	7	7%
-	-	-	52	52%
Total			100	100%

Table 5: Comparison of sensitivity, specificity and predictive values of Typhidot and Diazo diagnostic tests

	Sensitivity	Specificity	PPV	NPV
Typhidot (IgM+)	88.46% (69.8%-97.5%)	86.49% (76.5%-93.3%)	69.7% (55.9%-80.6%)	95.5% (88%-98.4%)
Diazo Test	73.08% (52.21%-88.43%)	79.73% (68.78%-88.19%)	55.8% (43.2%-67.8%)	89.4% (81.6%-94.1%)

It has been observed from the study that both the sensitivity (88.46%; CI=

69.8%-97.5%) and specificity (86.49% CI= 76.5%-93.3%) is higher for the Typhidot (IgM+) in comparison to the Diazo test. The positive predictive value (PPV) and the negative predictive value (NPV) was also observed to be higher in the Typhidot (IgM+) (PPV=69.7%; CI= 55.9%-80.6%), NPV=95.5%; CI= 88%-98.4%) in comparison to the Diazo test indicating the possibility of error in the detection of Typhoid using Typhidot was lower in comparison to Diazo test. Thus the study indicated that Typhidot is a better diagnostic test for detecting Typhoid in contrast to the Diazo test.

Discussion

Though typhoid fever is a common infection in children, it is difficult to diagnose because of its nonspecific symptoms and signs. However, it is necessary to diagnose early to initiate appropriate antibiotic therapy because a delay in starting antibiotic treatment may lead to several morbidities and even death. The gold standard for diagnosing typhoid fever has always been the blood culture method. Still, it is time-consuming, requires elaborate laboratory equipment and a level of technical expertise which may not be present in resource-poor laboratories. This delay may result in complications of typhoid fever.

The majority of the patients (50%) were in the age group of 6-10 years which is similar to the study done by Devaranavadagi RA et al. [7]. Where the most common age group was 5-10 years, in our study majority of children (46%) belonged to the lower class. This is in conjunction with the observation made by Rasaily R et al. [8], where most cases came from lower socio-economic classes with poor personal hygiene.

In our study, 26% of the cases were positive by blood culture, which is more or less comparable to the observations made by Retnosari S et al. [9] and Yadav et al. [10], who has reported 24% positivity and 28.5% positivity respectively for blood culture. The comparatively lower sensitivity of blood culture may be because of the ridiculous use of antimicrobial agents and difficulty drawing the required quantity of blood for cultures in children. It has been observed in the current study that 33% of the cases were positive by Typhidot M test, which is found to be consistent with 32.4% reported by Mehmood et al [11]. and 50.4% reported by Udayakumar et al [12].

In the present study that 34% of the cases are positive for diazo which is found to be between the values observed by Raman TSR et al. [13] and Tanyigna KB et al. [14].

In the present study, the sensitivity of the Typhidot was observed to be 88.46% which was found to be comparable to other previous studies. So Typhidot fulfils one of the standards for an ideal diagnostic test as it does not usually miss the diagnosis compared to Blood Culture. The specificity of the present study is 86.49% which is consistent with Udayakumaret al [12], Jabbar et al. [15]. and Sherwal et al. [5]. which reported specificity 84.6%, 87% and 87.5% respectively. The specificity of 86.49% was because Typhidot showed positive in only 10 of 74 Blood culture-negative cases.

The analysis of the observations in this study indicates that although blood culture is the gold standard for diagnosing typhoid fever, Typhidot assay might be a sensible alternative in developing countries because of its high sensitivity and specificity. The typhidot will be particularly helpful in those areas where facilities for doing a blood culture is not available.

The sensitivity of the Diazo test observed in our study is 73.08% which was found to be comparable to studies conducted by Shivpuri et al. [6], Beig FK et al. [16] and Nugraha et al. [17], who showed a sensitivity of 81%, 86.7% and 83% respectively. The sensitivity of 73.08% is that out of 26 blood culture positive typhoid cases, 19 were detected positive by Diazo test. The specificity of the present study is comparable with studies conducted by Raman TSR et al. [13] and Beig FK et al. [16], who showed a specificity of 83% and 85.7%, respectively. The specificity of 79.73% is because the Diazo test showed positive in only 15 out of 74 blood culture-negative cases.

It has been observed from the study that Typhidot has more sensitivity and specificity and a better positive predictive value and negative predictive value in comparison to the Diazo test, which is comparable with the results reported by Beig et al. [16], which showed Typhidot having sensitivity, specificity, PPV and NPV of 90%, 100 %, 100%, and 92.1% respectively. In contrast, Diazo test had sensitivity, specificity, PPV and NPV of 86.7%, 85.7%, 83.9%, 88.2% respectively.

Conclusion

The sensitivity and specificity of Typhidot are more compared to the Diazo test. Although Typhidot is superior to the Diazo test, the present study shows reasonable sensitivity and specificity value for the Diazo test. Hence it can be used in resource-poor settings as it is economical and easy to perform.

Limitations Of The Study: The sample size is smaller in this study. If more children were enrolled in the study, a more detailed picture of clinical and laboratory features could be obtained. Large scale prospective evaluation of Typhidot assay and Diazo test in endemic populations should be done to find the exact use of both tests.

Author's contribution

Dr Harisha Gopal: Acquisition and interpretation of data, data analysis, drafting the article, and literature review, Dr Sandeep B: Concept, interpretation of data and data analysis, drafting the article, and literature review, Dr Pooja Pradeep: Data analysis, manuscript review, manuscript editing, revising the article critically for important intellectual content. All the authors approved the final manuscript.

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