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Comparative Analysis of Vaccination Status in Enteric Fever: Correlating Clinical and Laboratory Parameters

Nixat Patel[1], Khyati Sasani[2*], Swapnil Shah[3]

[1]Governmaent Medical College, Surat, India
[2,3]Department of Pediatrics, Nirmal hospital, Surat city, India

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***Corresponding author**:
Dr. Khyati Sasani
Department of Pediatrics, Nirmal hospital, Surat city, India
E-mail: sasani.khyati@gmail.com

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ABSTRACT

Introduction: The emergence of resistant haplotypes of Salmonella makes control via vaccination an urgent priority. This study was conducted to evaluate the clinical and investigative profile of enteric fever cases admitted during study period at Nirmal hospital private limited, Surat and their typhoid immunization status to assess difference in presentation and clinic-investigation profile between immunized and unimmunized group.

Methodology: This cross-sectional study conducted among **c**hildren admitted with enteric fever. All the children were assessed for hepatitis vaccination status. Clinical and laboratory parameters were correlated with vaccination status.

Results: Out of 101 study subjects, only 19 (18.81%) were immunized with any of the typhoid vaccine. Signs-symptoms and complications were not associated with immunization status ($p > 0.05$). Lower hemoglobin level and higher WBC count were associated with immunization status ($p < 0.05$). The mean difference in Absolute Eosinophil Count was found statistically insignificant. (p 0.109) between two groups.

Conclusion: The enteric fever is more common in school going age group of 5-14 years of age. Vaccination against typhoid provides protection against infection with S. Typhi. Vaccination can also help to reduce anemia during episode of enteric fever.

INTRODUCTION

Enteric fever, commonly known amongst community as a typhoid fever is a severe multisystem illness basically of intestinal reticulo-endothelial system is characterized by the classic prolonged fever, sustained bacteremia and bacterial invasion and multiplication within the mononuclear phagocytic cells of the liver, spleen, lymph nodes and Peyer's patches of small intestine. Fever is caused by Infection in Intestinal lymphoid tissue hence known as an "Enteric Fever".[1] Enteric fever is a global health problem occurring in all parts of the world where there is substandard sanitation, poor personal hygiene and lower socio-economic strata with estimated 30 million new infections each year worldwide and 206,000 deaths. [2]

Improved standards of public health have resulted in a marked decline in incidence of typhoid fever in developed countries. Population based studies from urban population in India suggests that the incidence of typhoid fever is 2730 per 100,000 population per year in 0-4year old children, 1170 per 100,000 per year in 5-19-

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year age group and 110 per 100,000 per year in 20-40-year age group.[3]

Diagnosis of enteric fever is fraught with problems. History, physical findings and fever pattern are suggestive but can neither confirm nor exclude typhoid.[4] In cases of enteric fever, including infections with S. Typhi and S. Paratyphi A and B, it is often necessary to commence treatment before the results of laboratory sensitivity tests are available because serodiagnosis cannot be made in earlier phase of the disease. Hence, it is important to be aware of options and possible problems before starting treatment.[5]

90% cases of enteric fever are caused by Salmonella typhi, where disease is known as typhoid fever, while in rest 10% case Salmonella Paratyphi A, Paratyphi B and Paratyphi C have been encountered, where the disease is known as Paratyphoid fever.[2]

Typhoid vaccines: Typhoid vaccines are on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.[6] Total 3 types of vaccines are Ty21a (a live vaccine given by orally), Vi capsular polysaccharide vaccine (ViPS) (an injectable subunit vaccine), and Typhoid conjugated vaccine (TCV). They are about 30 to 70% effective for the first two years depending on the specific vaccine in question.[7]

The World Health Organization (WHO) recommends vaccinating all children in areas where the disease is endemic. Because inadvertent and inappropriate use of antibiotics has been leading to an emergence drug resistant halotypes of traditionally used flouroquinolones as well second line drugs. [8]

The emergence of resistant haplotypes of Salmonella makes control via vaccination an urgent priority. This study was conducted to evaluate the clinical and investigative profile of enteric fever cases admitted during study period at Nirmal hospital private limited, Surat and their typhoid immunization status to assess difference in presentation and clinic-investigation profile between immunized and unimmunized group.

Methodology

This study was a cross sectional study. This study was conducted among Children aged 1 to 18 years admitted with enteric fever in the year 2019-2020 at Nirmal hospital located in Surat city, India. comprise the study population.

All cases fulfilling inclusion criteria and admitted in the hospital during the study period were considered for the study.

Eligibility criteria:

Patients aged 1 to 18 years, hospitalized at Nirmal hospital and diagnosed having enteric fever were included in the study.

Patients with chronic illness/ immunocompromised state/on long term steroids/ on chemotherapy or immunotherapy, having other associated acute infections or documentation of vaccination was not available were excluded from the study.

Data collection: The data was gathered from patient's indoor case records and hospital files and available data of relevant vaccination. All the cases with positive Typhidot IgM, positive Widal test (rising titer or single titer of 1:160), positive Blood culture, or any of this three was included in study.

Permission was obtained from the hospital ethics committee for conducting the study. A detailed clinical history, a thorough clinical examination and laboratory investigations as required at the time of collection of data and did not involve deviation from standard care, no conflict of interest was identified on admission and during the course of hospital stay. The findings recorded in a premade proforma. Informed consent was obtained from the parents.

Immunization History: History of hepatitis vaccination including the type of vaccine administered, at which age (time since immunization), and whether the booster dose has been taken or not was analyzed.

Definition of variables:

Fever: Temperature of more than 99.9^0F.(Axillary temperature with digital thermometer)

Fever defervescence: Number of days required for fever to come less than 100^0F for 24 hours in the absence of antipyretic after starting antibiotic.

Hepatomegaly: The edge of the right lobe of liver palpated by clinician more than 2 cm below the right costal margin.[9]

Splenomegaly: The tip of the spleen is felt beyond 2 cm below the left costal margin, it is considered abnormal.[10]

SGPT was considered raised when the value was >100u/L. Positive Widal test was considered when Anti TO was more than equal to 1:80 and Anti TH was more than or equal to 1:160.

Classification of Anemia [11]: Based on the hemoglobin level, all cases were divided in to anemic (Hb <11gm%) and non-anemic group (Hb ≥ 11 gm%). Anemia further divided in to Mild (Hb 10-11gm%), Moderate (Hb 7-10 gm%), and Severe (Hb <7 gm%).

Eosinophil counts less than 30cells/µL is defined as Eosinophilia. Platelet count less than 1.5lac/mm^3 is defined as Thrombocytopenia. Neutrophil count less than 1500 cells/µL is defined as Neutropenia.[12]

Statistical method: Based on the history of immunization, the study subjects were divided in to two groups - Group 1 Cases with positive history of immunization; and Group 2 - Cases with no history of immunization. All presenting symptoms, clinical signs and laboratory in-

vestigations were compared between these two groups. Qualitative variables were presented as frequency and percentage and Quantitative data were presented as mean and standard deviation. Statistical significance for qualitative data was assessed by using Chi-square test and for quantitative variable unpaired t test was used to assess statistical significance. Statistical association was assessed at 95% confidence interval. P value of <0.05 was considered as statistically significant.

RESULTS

Total of 101 pediatric cases of enteric fever were enrolled in the present study. Out of 101 patients, 52 (51.49%) were males and 49 (48.51%) were females. Mean age of cases was 8.84 ± 3.12 years (Table 1).

Most common symptom was fever (100%) followed by abdominal pain (38.61%), anorexia (37.62%) and vomiting (37.62%). Most common sign was coated tongue which was found among 52 (51.49%) cases followed by toxic look in 21 (20.79%) cases. Hepatitis was found in 5 (4.95%) cases while intestinal perforation, meningitis and meningism were seen in one case each. Among 101 cases, 19 (18.81%) had mild anemia, 23 (22.77%) had moderate anemia and 2 (1.98%) had severe anemia. Among them, 7 (6.93%) had total leucocyte count less than 4000 while 15 (14.85%) had TLC more than 11000 (Table 2).

Out of 101 study subjects, only 19 (18.81%) were immunized with any of the typhoid vaccine. Out of 19 cases vaccinated for typhoid vaccine, 18 were immunized with typhoid polysaccharides vaccine while 1 patient had typhoid conjugated vaccine.

There was no significant difference found in signs and symptoms between immunized and non-immunized children. (p > 0.05) (Table 3). The mean hemoglobin level in immunized group was 12.1 (SD 1.4) mg/dl while it was 10.7 (SD 1.6) mg/dl in non-immunized group. Application of t test indicated that the in immunized group mean hemoglobulin was significantly higher than non immunised group. (p <0.001) The mean difference in TC level between these two groups was found statistically significant. (p 0.026).

Table 1: Socio-demographic profile of cases included in the study

Variables	Cases (n=101) (%)
Age in years	
1 – 4	17 (16.83)
5 – 9	48 (47.52)
10 – 14	27 (26.73)
15 – 18	9 (8.91)
Mean ± SD (years)	8.84 ± 3.12
Gender	
Male	52 (51.49)
Female	49 (48.51)

The mean difference in AEC between these two groups was found statistically insignificant. (p 0.109). There was no significant difference in complication rate between immunized and non-immunized cases. (p 0.66) Complications and Fever defervescence time are not associated with immunization status.

Table 2: Clinical and laboratory profile of cases included in the study

Variables	Cases (n=101) (%)
Symptoms	
Fever	101 (100)
Abdominal pain	39 (38.61)
Anorexia	38 (37.62)
Vomiting	38 (37.62)
Cough	34 (33.66)
Headache	15 (14.85)
Diarrhea	14 (13.86)
Duration of fever	
≤ 3 days	18 (17.82)
3-7 days	46 (45.54)
≥ 7 days	37 (36.63)
Signs	
Tongue coated	52 (51.49)
Toxic look	21 (20.79)
Hepatomegaly only	14 (13.86)
Pallor	5 (4.95)
Icterus	3 (2.97)
Hepatosplenomegaly	3 (2.97)
Neck rigidity	2 (1.98)
Splenomegaly only	1 (0.99)
Lab investigation	
Normal Hb (Hb ≥11 gm%)	57 (56.44)
Anemia(WHO classification)	44 (43.56)
Mild (Hb 10-11gm%)	19 (18.81)
Moderate (Hb 7-10 gm%)	23 (22.77)
Severe (Hb<7 gm%)	2 (1.98)
TC (per mm^3)	
<4000	7 (6.93)
4000-11000	79 (78.22)
>11,000	15 (14.85)
Eosinopenia (<30 cells/µL)	1 (0.99)
Neutropenia (<1500 cells/µL)	5 (4.95)
Thrombocytopenia (<1.5 lac/mm^3)	11 (10.89)
Complications	
Intestinal Perforation	1 (0.99)
Meningitis	1 (0.99)
Meningism	1 (0.99)
Hepatitis	5 (4.95)
Fever defervescence time	
≤ 3 days	37 (36.63)
3-7 days	60 (59.41)
≥ 7 days	4 (3.96)
Immunization status	
Immunized	19 (18.81)
Polysaccharide	18 (17.82)
Conjugated	1 (0.99)
Non-immunized	82 (81.19)

Table 3: Comparison of Clinical and laboratory profile between immunized and non-immunized cases

Variables	Immunised (n=19) (%)	Non-immunised (n=82) (%)	P value
Gender			
Male	10 (52.63)	42 (51.22)	0.911
Female	9 (47.37)	40 (48.78)	
Age in years (Mean ± SD)	7.86 ± 2.72	9.3 ± 4.93	0.222
Symptoms*			
Fever	19 (100)	82 (100)	-
Headache	3 (15.79)	12 (14.63)	0.898
Diarrhea	1 (5.26)	13 (15.85)	0.229
Vomiting	6 (31.58)	32 (39.02)	0.546
Abdominal pain	10 (52.63)	29 (35.37)	0.164
Cough	8 (42.11)	26 (31.71)	0.387
Anorexia	5 (26.32)	33 (40.24)	0.259
Signs			**P value**
Toxic look	3 (15.79)	18 (21.95)	0.551
Tongue coated	6 (31.58)	46 (56.1)	0.504
Hepatomegaly only	2 (10.53)	12 (14.63)	0.415
Spleenomegaly only	0 (0)	1 (1.22)	-
Hepatospleenomegaly	0 (0)	3 (3.66)	-
Neck rigidity	0 (0)	2 (2.44)	-
Pallor	0 (0)	5 (6.1)	-
Icterus	0 (0)	3 (3.66)	-
Lab investigations			
Hb (mg/dl) **(M ± SD)**	12.1 ± 1.40	10.7 ± 1.60	<0.001
WBC total count (cell/µL) **(M ± SD)**	6594 ± 1877.00	8261 ± 3094.00	0.026
Absolute Eosinophil Count (cell/µL) **(M ± SD)**	145.7 ± 55.10	181.3 ± 92.00	0.109
Complication			
Intestinal Perforation	0 (0)	1 (1.22)	
Meningitis	0 (0)	1 (1.22)	
Meningism	0 (0)	1 (1.22)	
Hepatitis	1 (5.26)	4 (4.88)	
Any complication$	1 (5.26)	7 (8.54)	0.66#
No complication	17 (89.47)	74 (90.24)	
Fever defervescence time			
≤ 3 days	6 (31.58)	31 (37.8)	0.256
3-7 days	11 (57.89)	49 (59.76)	
≥ 7 days	2 (10.53)	2 (2.44)	

*Cases with specific symptoms were compared with the cases without the same symptoms
$Any one of the above-mentioned complications.
#P value calculated by comparing any complications versus no complications.

DISCUSSION

Typhoid (enteric) fever is a significant cause of morbidity and mortality in pediatric age group. It is the infection with Salmonella enterica serovar Typhi (S. Typhi) and Paratyphi (S. Paratyphi), a gram-negative bacterium that attacks the body via the small intestines and inhabits macrophages in reticuloendothelial system of body, where it is shed into the bloodstream.[13,14]

Salmonella has become a major threat to the society due to the disease severity, recurrence of disease through carrier state, emergence of multidrug resistance and its use as a potential candidate in bioterrorism. [15,16] This demands for an effective prophylactic measures. WHO has explained the importance of vaccine against typhoid fever. Currently three licensed vaccines for typhoid fever – 1) Polysaccharide subunit (Vi PS), 2) live attenuated S. Typhi strain (Ty21a), 3) Typhoid conjugated vaccine are commercially available.

Out of 101 study subjects, only 19 (18.81%) were immunized with any of the typhoid vaccine. Out of 19 cases vaccinated for typhoid vaccine, 18 were immunized with typhoid polysaccharide vaccine while 1 patient had typhoid conjugated vaccine. For long, only available typhoid vaccine in India was Vi Polysaccharide vaccine. A new conjugate typhoid vaccine produced by Indian manufacturer was licensed in the country in 2008/2009. Till typhoid vaccine is not included in national immunization programme by Government of India.[17]

Comparison between immunized and non-immunized: Out of 19 immunized children, 52.63% were males while 47.37% were females. There is no such difference in ty-

phoid immunization between male and female gender. Out of 82 non-immunized children, 51.22% were males while 48.78% females. This indicate that there was no gender difference in the immunization coverage of typhoid vaccine in the society.

Among immunized almost 95% were between 5 years to 14 years of age. This type of trends is seen because typhoid vaccine is effective after the age of 2 years. Efficacy of vaccine is not established before the age of 2 years. [18, 19] Out of 82 non-immunized children, 17 (20.73%) were between 1-4 years of age, 40 (48.78%) were between 5-9 years of age, 17 (20.73%) were between 10-14 years of age, 8 (9.76%) were between 14-19 years of age. There was significant difference in the immunized and non-immunized children according to age groups.

Headache was seen 15.79% immunized children vs. 14.63% non-immunized children; diarrhea 5.26% vs. 15.85%; vomiting 31.58% vs. 39.02%; abdominal pain 52.63% vs. 35.37%; cough 42.11% vs. 31.71% and anorexia 26.32% vs. 40.24%. There was no significant difference found in symptoms between immunized and non-immunized children. ($p > 0.05$) This indicated that immunization status does not have any significant effect on clinical presentation of typhoid.

Out of 19 immunized children, 15.79% had toxic look, 31.58% had coated tongue and 10.53% had hepatomegaly. There was no significant difference found in signs between immunized and non-immunized children. ($p > 0.05$) Similar to the symptoms, clinical signs also did not significantly differ in immunized and non-immunized children.

In present study, out of 19 immunized children, only 1 child had complication in the form of hepatitis. While in non-immunized children, 4.88% had hepatitis while Intestinal Perforation, Meningitis and Meningism were seen in 1.22% cases. There was no significant difference between immunized and non-immunized cases. (p 0.66). As complications were rare in present study their rate doesn't differ much in immunized and non-immunized children.

In present study, mean difference in hemoglobin level and total count level between this two groups were found statistically significant. ($p <0.05$). In immunized children mean hemoglobin level is significantly more compared to non-immunized children. In non-immunized children TC count was significantly higher compared to immunized children.

Widal test was performed in 6 immunized children and 15 non-immunized children. Widal test was positive in 50% immunized children while it was positive in 73.3% non-immunized children. There was no significant difference between immunized and non-immunized cases. So, this indicates that Widal test result is not affected by immunization status of a child.

Typhidot test was performed in 8 immunized children and 58 non-immunized children. It was positive in 75% immunized and in 50% of non-immunized children. There was no significant difference between immunized and non-immunized cases. This indicates that Typhidot test result is not affected by immunization status of a child.

In present study, out of 19 immunized children, blood culture was positive in 7(36.84%) and negative in 12 (63.16%) children while out of 82 non-immunized children, it was positive in 68(82.92%) and negative in 14 (17.07%) children. Blood culture was found positive for S. Typhi in 53 (64.63%) non-immunized children while positive for S. Paratyphi A in 14 (17.07%) non-immunized children. Out of 19 immunized children blood culture was found positive for S. Typhi in 2(28.57%) and for S. Paratyphi A in 5(71.42%) patients. After confirming statistical significance, it is observed that blood culture report for S. Typhi was positive in significantly high number in non-immunized children as compared to immunized one.

Accurate diagnosis of typhoid fever at an early stage is important not only for diagnosis of etiological agent, but also to identify individuals that may serve as a potential carrier, who may be responsible for acute typhoid fever outbreaks. [20,21] Options for the diagnosis of typhoid fever are clinical signs and symptoms, serological markers, bacterial culture, antigen detection and DNA amplification.

CONCLUSION

From this study we conclude that the enteric fever is more common in school going age group of 5-14 years of age due to consumption of unhygienic food and water in school and from street vendors. Enteric fever can have varied presentation so high index of clinical suspicion is required in patient presenting as fever without focus for early diagnosis and treatment. Vaccination against typhoid provides protection against infection with S. Typhi. Vaccination can also help to reduce anemia during episode of enteric fever.

We recommend conducting larger multi-centric study, in order to get proper representative data and large sample size.

Limitations of the study

Small sample size due to short period of data collection may be one of the limitations. This study was conducted in private hospital so our patient population may not truly represent disease status in community. Patients who have already received antibiotic therapy prior to the samples being taken were also included which could have affected clinical and laboratory profile.

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