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Original Article

Typhoid fever in Dhulikhel hospital, Nepal

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Abstract
One hundred and twelve cases of typhoid fever presenting in outpatient and emergency department of Dhulikhel Hospital in Nepal were studied. In this study, it was found that 71% typhoid fever cases were less than 30 years of age group with male to female ratio of 3:1. Fever over 5 days followed by headache and chills were major presenting symptoms. Widal test and blood culture for *Salmonella typhi* were positive in 59% and 49% cases respectively. Two third of our study population had total leucocyte count of normal range. The fever clearance time was significantly better with ofloxacin compared to ciprofloxacin ($p<0.05$) and ceftriaxone compared to chloramphenicol ($p<0.05$). The release from treatment was significantly shorter with ceftriaxone compared to ofloxacin, ciprofloxacin and chloramphenicol ($p<0.01$). Ceftriaxone was found to be 100% sensitive to salmonella typhi. Amoxicillin was only 52.1% sensitive to *Salmonella typhi*. Early diagnosis and institution of appropriate antibiotic therapy is of paramount importance in the management of typhoid patients.

Key words: Typhoid fever, salmonella typhi, fever clearance time, release from treatment

Introduction

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%. In some developing countries of Asia and Africa the annual incidence may reach 1% with case fatality rate as high as 10%. About 70% of all fatalities from typhoid fever occur in Asia. This gives the global estimates of at least 16 million new cases of typhoid fever each year, with 600000 deaths[1,4,14].

Improved living conditions and the introduction of Chloramphenicol in 1948 resulted in a drastic reduction of cases and mortality due to typhoid fever in industrialized countries, however, the disease is still a significant public health problem in many parts of south and east Asia, Africa and South America[1,2,4]. Like in many tropical countries, typhoid fever remains a major public health issue in Nepal too. Although the situation varies greatly world–wide and the incidence of typhoid fever fluctuates from one year to another, it has been estimated that the highest burden of the disease is in Asia[3,4,5,6,16].

In Nepal typhoid fever is also known as "bisham joauro" meaning fever with poison. The fever is prevalent in mountains, valleys and southern belts of Nepal as an endemic disease with its peak incidence in May to August. Typhoid fever is one of the leading diagnoses of fever in most of the hospitals in Nepal[5,15]. Typhoid outbreak was responsible for the deaths of many Nepalis from the time it was known as one of the causes of the fever. However, typhoid fever was considered responsible for deaths of many patients admitted in the hospitals in Kathmandu, the capital of Nepal, in late 1960s when the National Public Health Laboratory (NPHL) came into being. There have been reports of seasonal typhoid outbreaks with recent one in 2002 in Bharatpur, a town in central Nepal. The multi-drug resistant typhoid epidemic in Bharatpur affected more than 6,000 patients in a 4- to 5- week period and was from a single source – the municipality water supply[5,6,7,10].

Typhoid fever is a systemic infection with the bacterium *Salmonella enterica* serotype *typhi*. This highly adapted, human-specific pathogen has evolved remarkable mechanisms for persistence in its host that help to ensure its survival and transmission. The fever is characterized by the classic prolonged fever, sustained bacteraemia without endothelial or endocardial involvement, and bacterial invasion of and multiplication within the mononuclear phagocytic cells of liver, spleen, lymph nodes, and peyer patches of the ileum[2,9,13].

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Materials and methods

This study was undertaken in Dhulikhel Hospital to have base line information on typhoid fever as regards to its demographic distribution, clinical features, laboratory findings and antibiotic response to help clinicians in future.

Total 112 cases of suspected typhoid fever attending to Dhulikhel Hospital were studied from November 2001 till October 2002. The diagnostic criteria of typhoid fever were based on clinical and laboratory findings. The clinical findings were – high grade fever over 5 days with headache, relative bradycardia, dry coated tongue and spleenomegaly. The laboratory findings were – no leucocytosis, blood culture positive for Salmonella and serotyping.

The febrile illness of other causes like pneumonia, malaria, deep abscesses, tuberculosis, amoebic liver abscess, encephalitis, influenza, endocarditis, visceral leishmaniasis, and connective-tissue diseases were excluded with necessary investigations. The demographic data, clinical parameter, laboratory findings and antibiotics and their response was analyzed.

Fever Clearance Time (FCT) was defined as the time from onset of treatment to the first time axillary temperature fell below 37˚C and remained below 37˚C for 48 hours.

Widal test: The slide test type of widal test was done to detect antibodies against O and H antigens of *S. typhi* and H antigens of *S. paratyphi* A and *S. paratyphi* B. The samples which showed agglutination (clumping) with the antigenic reagents were considered positive and those that do not agglutinated were considered negative.

Blood Culture: The blood culture bottles were immediately incubated at 37˚ C for at least 5 days. Further incubation was done in case it was indicated. Regular subculture was done on day 1 i.e. after overnight incubation and after 5 days of incubation on solid media namely Blood Agar (BA), MacConkey Agar (MA) and Chocolate Agar (CA). Subculture was also done when there was obvious turbidity in the broth on any day. Subcultures on BA and CA were incubated in the candle jar where as those on MA were incubated at ambient atmosphere.

Serological test: When the biochemical test of the isolate was characteristics of salmonella, serological agglutination test on a suspension of about 10^{10} bacteria per millilitre were carried out, first using polyvalent sera and if positive using monovalent sera as well, in the following order:

- Salmonella polyvalent O sera
- Individual salmonella O group sera
- Single factor H sera

Antibiotic sensitivities were carried out on all positive blood isolates using Kirby-Bauer disc diffusion method.

The statistical analysis was done with SPSS 11.5 for Microsoft windows. Mean values ± standard deviations were calculated for continuous variables. The statistical significance of differences between groups was analyzed by T – test for continuous variables.

Results

All 112 patients with typhoid fever had undergone routine blood test with widal test and blood culture. The age of the study population ranged from 6 years to 75 with mean ± standard deviation of 28.33±15.2. The male female ratio of study population was 3:1. Seventy one percent of the patients were of below 30 years of age.

Table 1: Age and Sex wise distribution of study population

Age group	Male	Female	Total
< 10	8	2	10
11 – 20	19	9	28
21 – 30	31	11	42
31 – 40	2	8	10
41 – 50	9	3	12
51 – 60	3	3	6
61 – 70	2	-	2
71 – 80	-	2	2
Total	74	38	112

Headache, chills, cough and pain were the common presenting symptoms at the time of admission significantly present along with fever.

Table 2: Symptom wise distribution of study population

Symptoms	No of Patient	Percentage
Fever	112	100
Headache	49	43.8
Chills	46	41.1
Vomiting	7	6.3
Cough	17	15.2
Pain Abdomen	12	10.7
Diarrhoea	9	8
Constipation	6	5.4
Disorientation	0	0

The widal test of 97 patients revealed that 59% were positive and 38% were negative. Regarding blood culture done in 112 patients, 49.2% were positive and rest were negative.

Table 3: Blood culture, widal test and spleenomegaly in study population

	Positive	Negative	Positive %
Widal	59	38	52.7
Blood Culture	55	57	49.2
Spleenomegaly	3	109	2.7

Spleenomegaly was found in 3 patients out of 112 patients.

Table 4: Total leucocyte count in study population

WBC count	No of patient	Percentage
< 4000	36	32.1
4000 - 11000	70	62.5
> 11000	6	5.3

Two third of the patients have total leucocyte count of normal range i.e. 4000 – 11000/cmm. Thirty two percent of the study populations have below normal leucocyte counts. Only 5.3% have raised leucocyte count.

Table 5: Response to different drugs

	No of patient	Fever clearance time	Release from treatment
Ciprofloxacin	57 (50.9%)	4.6±1.15	9.7±3.17
Ofloxacin	21 (18.8%)	3.7±0.91	9.7±2.88
Ceftriaxone	17 (15.2%)	4.1±0.89	6.6±1.23
Chloramphenicol	5 (4.5%)	5.4±0.89	10.4±1.14
Cefotaxime	4 (3.6%)	4.5±0.82	8±0.82
Amoxicillin	8 (7.1%)	6.2±1.03	6.8±2.6

The average fever clearance time was shortest with Ofloxacin - 3.7±0.91 (mean ± standard deviation) whereas longest with Amoxicillin group – 6.2±1.03. The release from treatment was shorter - 4.1±2.6with Amoxicillin whereas longest - with Chloramphenicol - 10.4±1.14.

The fever clearance time had no significant difference between ciprofloxacin and ceftriaxone (p - > 0.05), ofloxacin and ceftriaxone (p - > 0.05), ciprofloxacin and chloramphenicol (p - > 0.05). This was significantly better in ofloxacin compared to

ciprofloxacin (p - <0.05), ceftriaxone compared to chloramphenicol (p - < 0.05).

The release from treatment was significantly shorter with ceftriaxone compared to ciprofloxacin, ofloxacin, chloramphenicol (p - < 0.001).

Table 6: Sensitivity of different drugs to salmonella

	Sensitivity (%)	Intermediate (%)	Resistant (%)
Ciprofloxacin	94.5	1.9	3.6
Ofloxacin	98.1	1.9	-
Ceftriaxone	100	-	-
Chloramphenicol	92.7	3.6	3.6
Cefotaxime	69.1	16.3	14.5
Amoxicillin	52.7	9.1	38.2

The ceftriaxone was found to be 100 percent sensitive to salmonella typhi. The next most sensitive after ceftriaxone was Ofloxacin followed by Ciprofloxacin and Chloramphenicol. Amoxicillin had only 52.7% sensitivity.

Discussion

Nepal is one of the Typhoid endemic countries in Asia and is a hot bed of Enteric fever. Typhoid fever is most common in pre-school and school age children. In our study group 71.4% were of less than 30 years of age. Therefore early diagnosis and management of typhoid cases is economically beneficial as it affects the younger age group.

Fever with temperature above 38˚C (axillary temperature) for more than 5 days, headache and chills are the common presenting symptoms in typhoid fever in Dhulikhel Hospital. Similarly thirty percent of study population presented with gastrointestinal problems including abdominal pain and diarrhoea, which is similar to symptoms described in most of the textbooks and research articles[2,9].

In Dhulikhel Hospital where laboratory facilities to perform total leucocyte count, widal test and blood for culture and sensitivity exists, results of those tests are helpful to clinicians to establish the diagnosis and select appropriate antibiotic therapy. However, positive widal test and isolation of S*almonella typhi* in blood culture are lower than in some of the other studies carried out by Parry et. al. in Vietnam and Laos[12]. This could be due to inadequate amount of blood sample i.e. less than 10 ml drawn for the blood culture or random use of antibiotics before presenting to our hospital.

In this study, the response of the drugs to typhoid fever is signified with fever clearance time. This is less with Ofloxacin - 3.7±0.91 where as maximum in Amoxicillin group. The Ceftriaxone and Ciprofloxacin have also less fever control days. These findings are consistent with the sensitivity of the drugs toward salmonella. The Ofloxacin has 98.1% complete and 1.9% partial sensitivity. Amoxicillin has longer fever control days as shown by 52.7% sensitivity and 38.2% resistance. Chloramphenicol has still good response with salmonella as it has average fever control days of 5.4±0.89 which could be well explained by sensitivity of 92.7%[1,7,16].

In this study, fever clearance time had no significant difference between ciprofloxacin and ceftriaxone (p - > 0.05), ofloxacin and ceftriaxone (p - > 0.05), ciprofloxacin and chloramphenicol (p - > 0.05). The chloramphenicol had similar fever clearance time with ciprofloxacin which could be due to few numbers of cases. Fever clearance time was significantly better in ofloxacin compared to ciprofloxacin (p - <0.05) and ceftriaxone compared to chloramphenicol (p - <0.05). The release from treatment was significantly shorter with ceftriaxone compared to ciprofloxacin, ofloxacin, chloramphenicol (p - < 0.001).

The release from treatment was average of 10 days. It is shorter with Ceftriaxone group - 6.6±1.23. This could be because of good response to treatment and patient's refusal of parenteral access after control of fever. Ciprofloxacin and Ofloxacin group have average of 9.7 days. Few cases had shorter duration that is because of changing antibiotics to another because of poor response. In Amoxicillin group, the treatment is released on few days because of poor control of fever and switched onto other antibiotics.

Conclusion

Typhoid fever or acute febrile illness caused by *Salmonella typhi,* is an important cause of community-acquired septicemia, morbidity and

mortality in Nepal as in many Asian countries. In Dhulikhel Hospital, this is one of the top acute febrile illnesses presenting in the out patient and emergency departments. To avert the increasing morbidity and mortality from typhoid fever, clinicians and health workers need to work together to raise awareness about the risk factors of typhoid fever. In the mean time, early diagnosis and institution of appropriate antibiotic therapy is of paramount importance in the management of typhoid patients.

Typhoid fever is predominant in age group of 21 – 30 years. Fever over 5 days followed by headache and chills are major presenting symptoms. Widal test and blood culture for *Salmonella* are positive in 59% and 49% cases respectively. Two third of our study population has total leucocyte count of normal range. The fever clearance time is significantly better with ofloxacin compared to ciprofloxacin ($p<0.05$) and ceftriaxone compared to chloramphenicol ($p<0.05$). The release from treatment is significantly shorter with ceftriaxone compared to ofloxacin, ciprofloxacin and chloramphenicol ($p<0.01$). The ceftriaxone is found to be 100% sensitive to salmonella typhi. The amoxicillin is only 52.1% sensitive to salmonella typhi.

Although this study was undertaken to have base line information regarding acute febrile illnesses and typhoid cases in Dhulikhel Hospital, further research is recommended in future to prevent and control the typhoid cases easily and to develop cost effective treatment protocol.

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