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ORIGINAL RESEARCH

Assessment of outcome of oral doxycycline versus intravenous doxycycline for the treatment of uncomplicated scrub typhus in children at a tertiary care centre

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Abstract

Background: Scrub typhus is an acute febrile sickness caused by the bacterium Orientia tsutsugamushi. The present study was conducted to assess outcome of oral doxycycline versus intravenous doxycycline for the treatment of uncomplicated scrub typhus in children.

Materials & Methods: 80 children less than 15 years of age with typhus fever of both genders were divided into 2 groups of 40 each. Group I received oral doxycycline and group II received iv doxycycline. Parameters such as mean duration of symptoms before starting doxycycline, mean time of starting doxycycline after admission, clinical features and outcome were recorded.

Results: The mean duration of symptoms before starting doxycycline was 4.7 days in group I and 6.3 days in group II. The mean time of starting doxycycline after admission was 2.3 days in group I and 2.9 days in group II. The difference was significant (P< 0.05). Clinical features were eschar in 14 and 15, fever in 17 and 21, headache in 11 and 13, peripheral oedema in 13 and 20, hepatomegaly in 12 and 18 and splenomegaly in 9 and 10 patients in group I and group II respectively. The difference was significant (P< 0.05). The mean fever defervescence in group I was 29.5 hours and in group II was 28.1 hours. The incidence of delayed defervescence (>48 hours) was seen in 14 in group I and 7 in group II. The difference was significant (P< 0.05).

Conclusion: For the treatment of scrub typhus, oral and intravenous doxycycline work just as well. Because oral doxycycline is more affordable, more useful, and effective in treating scrub typhus, it ought to be the initial course of treatment.

Keywords: Scrub typhus, Eschar, Fever

Introduction

Scrub typhus is an acute febrile sickness caused by the bacterium Orientia tsutsugamushi. Other names for it include Chiggerborne typhus and Tsutsugamushi sickness. The arthropod trombiculid mite bite is the means by which this zoonotic infection is transmitted.[1]A papule appears at the bite site. Bite marks are frequently observed on the groin, axillae, neck, and genitalia. A dark eschar develops around the ulcerated papule as it heals. The initial signs and

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symptoms of the condition include fever, chills, headache, and myalgia.[2]It becomes exceedingly challenging for a paediatrician treating it to distinguish it from other illnesses such as leptospirosis, typhoid, malaria, and dengue. The disease's diagnostic characteristic, the eschar, is rare to observe. In India, it is one of the most common infections, and the number of cases is rising. It can cause complications such as meningoencephalitis, gastrointestinal hemorrhage, acute renal failure, and ultimately multiple organ failure if it is not identified and treated promptly.[3,4]

The first line of treatment for any clinically diagnosed case of scrub typhus is doxycycline, which is administered at a dose of 100 mg twice day for 5-7 days in adults and 3-5 mg/kg/day in children. Azithromycin is the backup medication if doxycycline is not appropriate or the patient is intolerant to it. The recommended dosage is 10 mg/kg/day for 4-5 days. Doxycycline used orally is easier to administer and more easily absorbed than when given intravenously, however it takes two to three hours for peak concentrations to be attained.[5]

Aims and objectives: The present study was conducted to assess the outcome of oral doxycycline versus intravenous doxycycline for the treatment of uncomplicated scrub typhus in children.

Materials and Methods

The present prospective observational study included 80 children less than 15 years of age with a diagnosis of typhus fever of both genders admitted to the paediatric emergency/OPD, Department of Paediatrics. Written consent from parents was obtained in order to take part in the study. The study was conducted from September 2019 to August 2020 at the Department of Paediatrics, Madhubani Medical College and Hospital, Madhubani, Bihar and from October 2020 to June 2021 at the Department of Paediatrics, Lord Buddha Koshi Medical College and Hospital, Saharsa, Bihar.

Keeping power (1-beta error) at 80% and confidence interval (1-alpha error) at 95%, the minimum sample size required was 60 patients; therefore, we included 80 (more than the minimum required number of cases) patients in the present study. Inclusion criteria: During the study period, all children under 15 years old who had a diagnosis of scrub typhus and were receiving monotherapy treatment with either oral or intravenous doxycycline were included. Scrub typhus was diagnosed based on the presence of a characteristic eschar and/or a positive immunoglobulin M (IgM) ELISA result. Exclusion criteria: Children with alternative diagnoses, such as co-infections, typhoid, dengue, malaria, or kala-azar, were excluded. Scrub typhus was diagnosed based on the presence of a distinctive eschar and/or a positive immunoglobulin (IgM) ELISA result. Data such as name, age, gender, etc. was recorded. Patients were divided into two groups of 40 each. Group I received oral doxycycline, and group II received intravenous (i.v.) doxycycline. Parameters such as mean duration of symptoms before starting doxycycline, mean time of starting doxycycline after admission, clinical features, and outcome were recorded.

Statistical analysis

The data thus obtained were subjected to statistical analysis using Statistical Package for the Social Sciences (SPSS) software version 22.0 and Microsoft 16. The mean and standard deviation (SD) are used to present descriptive data. The Chi-square test, or Fischer's exact test, was used to compare dichotomous variables, and the t-test, or Mann-Whitney test, was applied for continuous data when appropriate. The nominal variable, gender, was compared using the Chi-square test. A P value < 0.05 was considered significant.

Results

Serology was used to diagnose scrub typhus in 80 (39.60%) of the 202 children under the age of 15 who developed an acute febrile illness during the study period.

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Table I: Demographic parameters of patients with scrub typhus

Parameters	Group I (n=40)	Group II(n=40)	P value
Mean age (in years)	10.02±2.03	9.52±2.08	0.62
Gender (Male/Female)	24/16	27/13	0.51
Mean duration of symptoms before starting doxycycline (in days)	5.01±1.60	6.95±2.73	0.43
Mean time of starting doxycycline after admission (in days)	2.50±1.3	2.97±1.84	0.01

In the current study, males were more prevalent in both groups, with a mean age of 10.02±2.03 years in the oral doxycycline group and 9.52±2.08 years in the intravenous doxycycline group at presentation. The average duration of fever at presentation was five days. The mean time of starting doxycycline was 2.50±1.3 days in the oral group and 2.97±1.84 days in the intravenous group [Table 1].

Figure 1: Gender wise distribution of patients

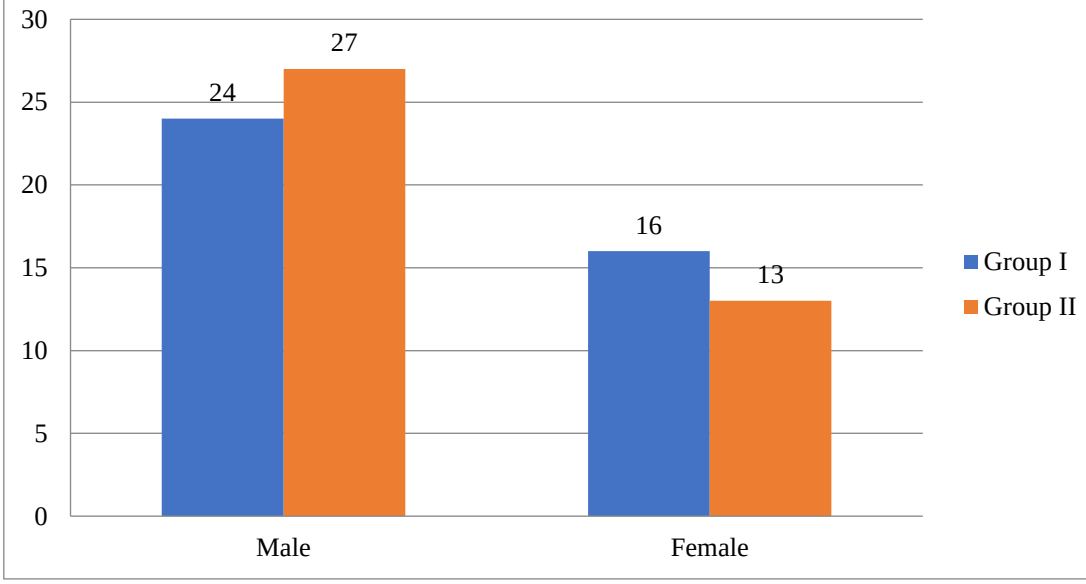

Table II: Assessment of parameters

Parameters	Group I (n=40)	Group II(n=40)	P value
Mean duration of symptoms before starting doxycycline (days)	4.7	6.3	0.01
mean time of starting doxycycline after admission (days)	2.3	2.9	0.09

Table II, shows that mean duration of symptoms before starting doxycycline was 4.7 days in group I and 6.3 days in group II. The mean time of starting doxycycline after admission was 2.3 days in group I and 2.9 days in group II. The difference was significant (P< 0.05).

Table III: Assessment of Baseline clinical features of patients with scrub typhus

Clinical features	Group I(n=40)	Group II(n=40)	P value
Fever	40 (100%)	40 (100%)	0.92
Eschar	26 (65%)	29 (72.5%)	
Skin Rash	12 (30%)	14 (35%)	
Headache	22 (55%)	19 (47.5%)	

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Peripheral oedema	27 (67.5%)	29 (72.5%)	
Hepatomegaly	37 (92.5%)	38 ((95%)	
Splenomegaly	33 (82.5%)	35 (87.5%)	

Table III, shows clinical features of patients; fever was reported in 100% of patients in both group.

Eschar was 65% and 72.5% in group I and group II respectively. Headache was reported in 55% in group I and 47.5% in group II of patients, slightly more prevalent in the oral group compared to the intravenous group. No significant difference was found regarding clinical parameters between the oral and intravenous doxycycline groups. The difference was not significant (P >0.05).

Table IV: Assessment of outcome

Outcome	Group I(n=40)	Group II(n=40)	P value
Fever defervescence (hours)	29.5	28.1	0.92
Incidence of delayed defervescence (>48 hours)	14	7	0.01

Table IV shows that the mean fever defervescence in group I was 29.5 hours and in group II was 28.1 hours. The incidence of delayed defervescence (>48 hours) was seen in 14 in group I and 7 in group II. The difference was significant (P< 0.05).

Discussion

Scrub typhus, first described in Japan in 1899, caused by Orientia tsutsugamushi (formerly Rickettsia), is an acute infectious disease of variable severity that is transmitted to humans by an arthropod vector of the Trombiculidae family.[6] It affects people of all ages, including children. Humans are accidental hosts of this zoonotic disease.[7,8] While scrub typhus is confined geographically to the Asia-Pacific region, a billion people are at risk, and nearly a million cases are reported every year. Mortality rates for scrub typhus range from < 1% to 50% depending on proper antibiotic treatment, the status of the individual infected, and the strain of O. tsutsugamushi encountered.[9,10] The present study was conducted to assess the outcome of oral doxycycline versus intravenous doxycycline for the treatment of uncomplicated scrub typhus in children.

The children in the current study had an average age of 10.02±2.03 years in group I and 9.52±2.08 years in group II, respectively. Seventy-five percent of them were between the ages of six and fifteen. These findings are consistent with a study conducted in North India by Kumar Bhat N et al.[7]

We found that the mean duration of symptoms before starting doxycycline was 4.7 days in group I and 6.3 days in group II. The mean time for starting doxycycline after admission was 2.3 days in group I and 2.9 days in group II. Varmaet al.[11] assessed the efficacy of intravenous versus oral doxycycline in managing uncomplicated scrub typhus. Out of a total of 178 children diagnosed with scrub typhus during the study period, 102 children who received either oral or intravenous doxycycline as monotherapy were included. The primary outcome measures studied were the incidence of delayed defervescence and the time of defervescence. The mean age of children treated with oral doxycycline was 9.5 ± 2.7 years and with i.v. doxycycline was 8.2 ± 2.4 years. Among the 178 children diagnosed with scrub typhus, 102 (57.3%) children treated with doxycycline alone were included in the study. Out of these, 78 (76.4%) cases received oral doxycycline, while 28 (27.4%) cases received intravenous doxycycline. There was no statistically significant difference in the response rate between the two groups. The p-value for time to defervescence was 0.672, and the p-value for the incidence of delayed defervescence was 0.984.

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We observed that clinical features were eschar in 14 and 15, fever in 17 and 21, headache in 11 and 13, peripheral oedema in 13 and 20, hepatomegaly in 12 and 18, and splenomegaly in 9 and 10 patients in groups I and II, respectively. We observed that the mean fever defervescence in group I was 29.5 hours and in group II was 28.1 hours. The incidence of delayed defervescence (>48 hours) was seen in 14 in group I and 7 in group II. Huang et al.[12] found that in their study of twenty-eight paediatric cases of scrub typhus, the majority of the children (60.7%) diagnosed with scrub typhus were male. Approximately half the patients were < 5 years old, and the mean age (SD) was 6.1 (3.66) years. Patients were more likely to live in rural rather than urban areas. The greatest number of cases was seen in the spring and summer. The primary clinical symptoms included fever (100%), cough (50%), eschar (50%), rash (35.7%), poor appetite (42.9%), lymphadenopathy (42.9%), headache (39.3%), and hepatomegaly (35.7%). AC-reactive protein (CRP) was elevated in 100%, aspartate aminotransferase (AST) was elevated in 100%, an alanine aminotransferase (ALT) level was elevated in 91.3%, hypoalbuminemia was found in 88.9%, and proteinuria in 50%. The mean (SD) duration of antibiotics was 11.0 (2.68) days, and the mean (SD) duration for fever resolution after treatment was 2.8 (2.51) days. Meningoencephalitis was noted in six patients. Our case series had no mortalities. These results suggest that a diagnosis of scrub typhus should be suspected in children with fever and laboratory evidence of liver dysfunction that live in rural eastern Taiwan.

Limitations of the study

The limitation of the study is the small sample size and short duration of study.

Conclusion

The authors found that for the treatment of scrub typhus, oral and intravenous doxycycline work just as well. Because oral doxycycline is more affordable, more useful, and effective in treating scrub typhus, it ought to be the initial course of treatment.

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