

Efficacy of Oral Doxycycline versus Intravenous Doxycycline for the Treatment of Uncomplicated Scrub Typhus in Children: A Prospective Interventional Study

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ABSTRACT

Introduction: *Orientia tsutsugamushi* causes acute febrile illness known as scrub typhus, which is spread by the bite of the trombiculid mite. Doxycycline is the first-line treatment for clinically diagnosed cases of scrub typhus. If not diagnosed and treated early, it can lead to complications such as acute renal failure, meningoencephalitis, gastrointestinal bleeding, and multiple organ failure. However, there have been no trials comparing the effectiveness of oral and Intravenous (i.v.) doxycycline for scrub typhus treatment.

Aim: To assess the efficacy of intravenous versus oral doxycycline in managing uncomplicated scrub typhus.

Materials and Methods: This prospective interventional research was conducted in the Paediatrics Department at Maharajah's Institute of Medical Sciences, Vizianagaram, India, from June 2021 to July 2022. 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 t-test or Mann-Whitney test was applied for continuous data, and the Chi-square test or Fischer's-exact test was used to compare dichotomous variables.

Results: 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 0.9845.

Conclusion: Both oral and intravenous forms of doxycycline demonstrated similar efficacy in the treatment of scrub typhus. Nearly all children in both groups became afebrile within 72 hours after starting treatment.

Keywords: Defervescence, Eschar, Febrile illness, *Orientia tsutsugamushi*

INTRODUCTION

Orientia tsutsugamushi is the bacteria that causes the acute febrile illness known as scrub typhus. Tsutsugamushi illness and Chigger-borne typhus are other names for it. It is a zoonotic infection that is spread by the bite of the arthropod trombiculid mite. At the site of the bite, a papule forms. Bites are commonly found on the neck, genitalia, axillae, and groin. As the papule heals, a black eschar forms around the ulcerated papule. Early clinical symptoms are characterised by fever, chills, headache, and myalgia [1,2].

It becomes very difficult for a treating paediatrician to differentiate it from other diseases like typhoid, malaria, dengue, and leptospirosis. The eschar is the diagnostic feature of the disease, but it is seen in very few cases. It is one of the most emerging infections in India, and the number of patients is increasing [1,2]. If not diagnosed and treated early, it can lead to complications that include acute renal failure, meningoencephalitis, gastrointestinal bleeding, and ultimately multiple organ failures [2].

Blood counts for scrub typhus may show early lymphopaenia with late lymphocytosis and thrombocytopenia. Scrub typhus frequently manifests as an undifferentiated fever that requires laboratory confirmation for diagnosis. In the lab, scrub typhus can be identified using molecular diagnostics, serology, and organism isolation. The Weil-Felix test, indirect immunofluorescent test, and Enzyme-linked Immunosorbent Assay (ELISA) are a few serological assays available for diagnosis [3].

Doxycycline, with a dose of 100 mg twice daily for 5-7 days for adults and 3-5 mg/kg/day for children, is the first line of treatment for any clinically diagnosed case of scrub typhus. If doxycycline is contraindicated or the patient is intolerant to it, the second choice is azithromycin, with a dose of 10 mg/kg/day for 4-5 days [4,5]. Orally administered doxycycline is more readily absorbed and more convenient to administer than intravenous doxycycline, but it takes two to three hours for peak concentrations to be reached [5].

Studies comparing the effectiveness of oral and intravenous doxycycline for the treatment of scrub typhus are scarce. Therefore, the primary objective of the present study was to assess the effectiveness of intravenous versus oral doxycycline in the management of scrub typhus.

MATERIALS AND METHODS

This prospective interventional research was conducted in the Paediatrics Department at Maharajah's Institute of Medical Sciences, Vizianagaram, India from June 2021 to July 2022. The study commenced after obtaining Ethical Committee approval (approval no: IEC/97/21).

Inclusion criteria: All children aged less than 15 years, diagnosed with scrub typhus, and treated with either oral or intravenous doxycycline as monotherapy within the study duration were included. The diagnosis of scrub typhus was confirmed by a positive Immunoglobulin M (IgM) ELISA result and/or the presence of a distinctive eschar [Table/Fig-1,2] [6].



[Table/Fig-1]: Typical eschar seen in scrub typhus indicates site of infection by the trombiculid mite. The lesion generally upto 1 cm in diameter, consists of central tough black scab peripherally slightly elevated red areola which is painless.



[Table/Fig-2]: Bilateral pedal oedema which was peripheral oedema seen in rickettsial disease.

Exclusion criteria: Children with alternative diagnosis such as malaria, typhoid, dengue, kala-azar, and co-infections were excluded.

Study Procedure

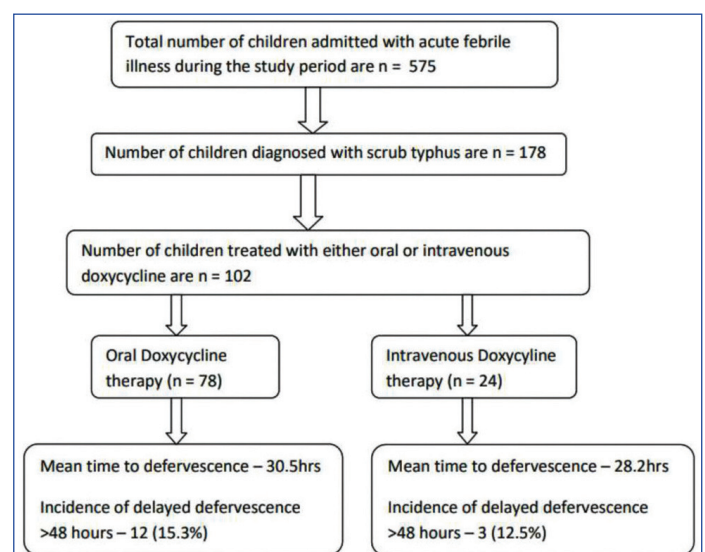
Baseline data including age, gender, duration of fever, co-morbidities, presence of an eschar, laboratory tests, and organ failure were collected from all study subjects. The study patients received either oral or intravenous doxycycline as monotherapy with a dose of 3-5 mg/kg/day for children [6]. Antimicrobial therapy was administered for seven days. All patients were monitored until their fever subsided. The principal investigator had no involvement in initiating or changing the treatment plan; the antibiotic therapy was decided by the treating paediatrician. The main outcome measures studied were the incidence of delayed defervescence (fever continuing 48 hours after starting appropriate antibiotic medication) and the time of defervescence (first day of axillary body temperature not exceeding 37.7°C (100°F) for more than three consecutive days without the use of antipyretics) [7].

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences (IBM Corp, released 2015, IBM SPSS, Version 23.0, Armonk) was used to conduct the statistical analysis. Descriptive data are presented as the mean and Standard Deviation (SD). When appropriate, the t-test or Mann-Whitney test was applied for continuous data, and the Chi-square test or Fischer's-exact test was used to compare dichotomous variables. A two-sided p-value of 0.05 or less was considered statistically significant for all tests.

RESULTS

Out of the 575 children who had acute febrile illness during the study period, 178 (30.9%) children were diagnosed with scrub typhus based on serology. Among them, 102 (57.3%) children were treated with either oral or intravenous doxycycline, while the remaining 76 (42.7%) children received alternative drugs such as azithromycin, as determined by the treating paediatrician. Oral doxycycline was administered in 78 (76.4%) cases, while intravenous doxycycline was given in 24 (23.6%) cases [Table/Fig-3]. There was an unequal distribution in sample size between the two groups, as intravenous doxycycline was only given to patients who were unable to comply with or take oral medications.



[Table/Fig-3]: Flowchart of the study.

In the present study, males were more prevalent in both groups, with a mean age of 9.5±2.7 years in the oral doxycycline group and 8.2±2.4 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 2.1±1.5 days in the oral group and 2.8±1.8 days in the intravenous group [Table/Fig-4].

Demographic characteristics	Oral doxycycline (n=78)	i.v. Doxycycline (n=24)	p-value
Mean age in years	9.5±2.7	8.2±2.4	0.4235
Gender (male/female)	51/27	16/8	0.418
Mean duration of symptoms before starting doxycycline	4.8±2.1 days	6.2±2.9 days	0.0054
Mean time of starting doxycycline after admission	2.1±1.5 days	2.8±1.8 days	0.0298

[Table/Fig-4]: Baseline demographic characteristics of patients with scrub typhus.

Headache was reported in 52% of patients, slightly more prevalent in the oral group compared to the intravenous group. No significant difference was found regarding co-morbidities or clinical parameters between the oral and intravenous doxycycline groups [Table/Fig-5].

Variables	Oral doxycycline (n=78)	i.v. Doxycycline (n=24)	p-value
Clinical profile			
Fever	78 (100%)	24 (100%)	1
Skin Rash	22 (28.2%)	8 (33.3%)	0.39
Eschar	50 (64.1%)	17 (70.8%)	0.299
Headache	40 (51.2%)	12 (50%)	0.451
Peripheral oedema	50 (64.1%)	17 (70.8%)	0.299
Hepatomegaly	70 (89.7%)	23 (95.8%)	0.185
Splenomegaly	64 (82%)	21 (87.5%)	0.260
Sequential organ dysfunction after starting treatment	2 (2.5%)	1 (4.1%)	0.478

[Table/Fig-5]: Baseline clinical features of patients with scrub typhus. Chi-square test

Thrombocytopenia and leukocytosis were observed in most participants, which are characteristic findings of this disease. Elevated levels of transaminases and alkaline phosphatase indicated hepatic involvement [Table/Fig-6].

Laboratory profile (Mean±SD)	Oral doxycycline (n=78)	i.v. Doxycycline (n=24)	p-value
Haemoglobin, (gm%)	10.8±1.1	10.5±1.5	0.8559
Total leukocyte counts, (per mm ³)	7400±3200	5400±2600	0.0063
Platelet count, (per mm ³)	168000±82000	128000±64000	0.0308
SGOT, (IU/L)	108.6±102	110.2±68	0.9428
SGPT, (IU/L)	98.2±82	96.5±63	0.9258
Creatinine, (mg/dL)	0.8±0.2	0.8±0.3	1

[Table/Fig-6]: Baseline laboratory findings of patients with scrub typhus. SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serumglutamic pyruvic transaminase

Both oral and intravenous doxycycline were equally effective in treating scrub typhus, with a response rate of 100% in both groups. Among patients treated with intravenous doxycycline, the average duration of defervescence was 28.2 hours (range: 4-126 hours), while in cases treated with oral doxycycline, the average defervescence time was 30.5 hours (range: 4-148 hours). However, there was no significant difference in the defervescence duration between the groups (p-value=0.9845). Within 72 hours of initiating either oral or intravenous doxycycline, nearly all children (96%) became afebrile [Table/Fig-7].

Outcome	Oral doxycycline (n=78)	i.v. Doxycycline (n=24)	p-value
Response rate (%)	100	100	1
Fever defervescence, (hours) {Mean (SD)}	30.5 (23.5)	28.2 (22.2)	0.672
Incidence of delayed defervescence (>48 hours), Number (%)	12 (15.3%)	3 (12.5%)	0.9845

[Table/Fig-7]: Shows primary outcomes of the current study.

DISCUSSION

The average age of the children in the current study was nine years, with 75 percent of them falling between the ages of six and 16, similar to the results of a study from North India by Kumar Bhat N et al., (2014) [8]. Fever was present in every patient in the current study, which was comparable to the findings of recent studies by Kumar Bhat N et al., and Palanivel S et al., [8,9]. Ninety-three percent of patients had hepatomegaly, while 68 percent had oedema and eschar each. Oedema has been documented in two studies from India, ranging from 37 percent to 60 percent [8,9]. The current study's lymphadenopathy rate of 12.5 percent was nearly the same as that of Kumar R et al.'s study in Sri Lanka, while De Silva N et al., observed a high frequency of lymphadenopathy in their study [10,11].

A few studies have documented the presence of eschar in 50-80 percent of scrub typhus cases [12,13]. On the other hand, several publications have documented cases of scrub typhus even in the absence of eschar. In previous research, rashes were shown in 15-91 percent of patients, whereas in the present analysis, rashes were only seen in 15 percent of cases [12]. When a child has fever, thrombocytopenia, and renal impairment, the development of eschar can be a helpful clinical sign in ruling out dengue infection in scrub typhus patients [14].

One of the earliest antibiotics used that decreased mortality and morbidity was chloramphenicol. According to a recent Cochrane review (2018), tetracycline, doxycycline, azithromycin, and rifampicin are effective medications for the treatment of scrub typhus, and there may be little or no side-effects [15]. In the same Cochrane review, it was found that tetracycline, doxycycline, azithromycin, and rifampicin are all effective medications for treating scrub typhus, and there may not be much of a difference between tetracycline, doxycycline, and azithromycin. The review also discovered that the aforementioned medications had relatively few treatment failures.

The majority of the children in the current trial who received doxycycline had a positive clinical outcome. A comparable clinical response to doxycycline has also been demonstrated in earlier studies [12-16]. Both oral and intravenous doxycycline treatments had comparable response rates and times to defervescence. Taking oral doxycycline was simple and had no catheter-related side-effects. Furthermore, the oral formulation was significantly less expensive than the intravenous form. Intravenous doxycycline is not more efficacious than oral doxycycline, except in children who are unable to take oral medication.

In a study that included patients affected by co-infections, a longer time to defervescence was observed [17]. The timing of doxycycline antibiotic medication after admission is related to prolonged hospital stays. It was reasonable to assume that delayed administration of doxycycline after admission could lengthen hospitalisation because nearly all individuals responding to oral doxycycline or intravenous doxycycline turned afebrile within three days. In another study, patients with scrub typhus who had jaundice, no headache, or relative bradycardia experienced delayed defervescence despite taking doxycycline [18].

The study's advantages include its large sample size, which included a comparable number of patients in both groups, and the fact that it was the first to compare oral and intravenous doxycycline for the treatment of scrub typhus.

Limitation(s)

The research was limited by the lack of information on pathogen strains and the inability to regulate the selection criteria for therapy regimens. Different intervals used for testing vital signs could have

led to errors because the instant when the patient's vital signs were checked was chosen to estimate the time to defervescence.

CONCLUSION(S)

The current study does show that oral doxycycline is equally effective as intravenous doxycycline for the treatment of scrub typhus. Therefore, oral doxycycline should be considered as the first line of treatment for scrub typhus since it is less expensive, more practical, and avoids the complications associated with venous catheter insertion. The authors strongly encourage further studies like this to promote the use of oral antibiotics in infections that can be managed with oral medications, thus preventing the overuse of intravenous antibiotics.

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