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Original Research Article

Comparison of Oral Doxycycline and Azithromycin Effectiveness in Scrub Typhus: An Observational study

Vignesh S.[1], Swetha H. [2], Pagadpally Srinivas[3]

[1,2,3]Vinayaka Missions Medical College and Hospital, Karaikal, Pondicherry

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Corresponding author: Dr. Vignesh S.

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Abstract

Background: Scrub typhus, a mite-borne infectious disease caused by Orientia tsutsugamushi, is a significant cause of acute febrile illness in endemic regions, particularly in Asia. Despite the availability of antibiotics, the optimal treatment regimen in pediatric patients remains a subject of ongoing research.

Objective: To compare the efficacy of doxycycline and azithromycin in the treatment of scrub typhus.

Methods: This study was conducted on 20 pediatric patients (≤12 years of age) presenting with fever lasting for seven or more days and confirmed scrub typhus infection in the Department of Paediatrics at Vinayaka Missions Medical College & Hospital, Karaikal, Puducherry.

Results: The study included 20 pediatric patients diagnosed with scrub typhus, with 10 receiving azithromycin and 10 receiving doxycycline. The mean age of patients was comparable between the two groups, with no statistically significant difference (P = 0.098). Gender distribution was also similar, with the azithromycin group comprising seven males and three females, while the doxycycline group had five males and five females (P = 0.361). The mean fever clearance time was significantly longer in the azithromycin group (53.1 hours, SD: 2.0) compared to the doxycycline group (44.2 hours, SD: 2.1), with a statistically significant difference (P = 0.001). The mean duration of hospital stay was slightly longer in the azithromycin group (46.2 hours, SD: 4.0) compared to the doxycycline group (45.2 hours, SD: 4.2), but this difference was not statistically significant (P = 0.317). No mortality was reported in either treatment group (P = 1.000). However, adverse drug reactions were observed in two patients (20.0%) in the azithromycin group, while none were reported in the doxycycline group, a statistically significant finding (P = 0.045). These results indicate that doxycycline was more effective in achieving faster fever resolution and had fewer adverse drug reactions than azithromycin.

Conclusion: Doxycycline is more efficacious in achieving fever defervescence and in preventing adverse drug reactions in patients with scrub typhus.

Keywords: Scrub typhus, Azithromycin, Doxycycline, Febrile illness, IgM ELISA, India.

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Introduction

Scrub typhus is a mite-borne infection caused by Orientia tsutsugamushi and is a leading cause of acute febrile illness in the Asian population.[1] It is estimated that scrub typhus affects approximately one million individuals globally each year, with a wide spectrum of clinical presentations ranging from mild febrile illness to life-threatening complications such as multiorgan dysfunction, shock, and acute respiratory distress syndrome (ARDS).[2, 3]

The disease is endemic in the Asia-Pacific region, including India, where it is a re-emerging infectious disease prevalent in several states such as Tamil Nadu, Karnataka, Kerala, Bihar, and the sub-Himalayan belt.[4] The burden of scrub typhus is increasing, making early diagnosis and effective treatment crucial in reducing morbidity and mortality. The clinical manifestations of scrub typhus are often nonspecific, including fever, headache, myalgia, cough, and gastrointestinal symptoms, which can lead to diagnostic challenges.[5, 6] A highly suggestive feature is the presence of an eschar at the site of the mite bite; however, its absence does not rule out the infection. If left untreated, scrub typhus has a median mortality rate of 6%, which significantly decreases to 1.4% with appropriate antibiotic therapy.[7] Given the potentially severe disease course, prompt treatment with effective antibiotics is essential.

Historically, scrub typhus was treated with chloramphenicol, but its use has declined due to concerns over toxicity, including bone marrow

suppression.[8] Currently, tetracyclines, particularly doxycycline, are the mainstay of treatment, while macrolides such as azithromycin have emerged as alternative options, especially in cases where tetracyclines are contraindicated, such as in children and pregnant women.[9, 10] Several studies have examined the efficacy of these antibiotics. Some findings suggest that a single dose of 500 mg azithromycin is as effective as a seven-day course of 200 mg doxycycline.[11] Another study indicated that a three-day regimen of azithromycin resulted in fever resolution similar to a seven-day course of doxycycline.[12] However, variations in study designs and treatment protocols highlight the need for more comprehensive data to determine the optimal therapeutic regimen for scrub typhus.

This study aims to compare the efficacy of doxycycline and azithromycin in the treatment of scrub typhus by evaluating fever clearance time, duration of hospital stay, and treatment-related outcomes, including mortality and adverse effects. The findings from this study will contribute to evidence-based recommendations for the most effective treatment strategy, ultimately improving patient outcomes and aiding clinicians in making informed therapeutic decisions.

Materials and Methods

This study was conducted on 20 pediatric patients (≤12 years of age) presenting with fever lasting for seven or more days and confirmed scrub typhus infection based on a positive IgM enzyme-linked immunosorbent assay (ELISA) test.[13] The study was carried out in the Department of Paediatrics at Vinayaka Missions Medical College & Hospital, Karaikal, and Puducherry. Patients were allocated to receive either azithromycin or doxycycline for treatment. The azithromycin group received a dosage of 10 mg/kg per day orally, administered once daily for seven days. The doxycycline group received weight-based dosing, with children weighing less than 40 kg receiving 4 mg/kg per day in two divided doses, and those weighing 40 kg or more receiving 100 mg twice daily for seven days.

Patients who had received antibiotic treatment before diagnosis or those who were noncompliant with the prescribed treatment were excluded from the study. The primary outcome measure was fever clearance time (FCT), defined as the time from the administration of the first antibiotic dose to the point when body temperature dropped to ≤37.5°C and remained so for at least 24 hours without recurrence. Secondary outcome measures included mortality during the treatment or follow-up period and treatment-related adverse effects. The duration of hospitalization was also recorded for comparison between the two groups. Adverse drug reactions, if any, were systematically documented and evaluated for both treatment arms.

Statistical Analysis: The data obtained was manually entered into Microsoft Excel and analysed using Statistical Package for Social Sciences (SPSS) v23. All the categorical variables were summarised using frequencies and percentages. Continuous variables were summarized using mean (standard deviation) (based on the results of data normality, tested using Kolmogorov–Smirnov test and the Shapiro–Wilk test). To test for statistical significance, Chi square test or Fisher exact test (for categorical variables) and independent 't' test (for continuous variables) was used. Statistical significance was considered at p value less than 0.05.

Results

The study included 20 pediatric patients, with 10 patients receiving azithromycin and 10 receiving doxycycline. The mean age of patients in the azithromycin group was 6.7 years (SD: 3.1), while in the doxycycline group, it was 6.9 years (SD: 3.0), with no statistically significant difference between the groups (P = 0.098). In terms of gender distribution, the azithromycin group had seven male patients and three female patients, whereas the doxycycline group had five males and five females. The difference in gender distribution between the two groups was not statistically significant (P = 0.361). No statistically significant differences were observed in the baseline characteristics of the study groups, ensuring comparability in the evaluation of treatment outcomes.

In the study, the mean fever clearance time was significantly longer in the azithromycin group (53.1 hours, SD: 2.0) compared to the doxycycline group (44.2 hours, SD: 2.1), with a statistically significant difference (P = 0.001). The mean duration of hospital stay was slightly longer in the azithromycin group (46.2 hours, SD: 4.0) compared to the doxycycline group (45.2 hours, SD: 4.2); however, this difference was not statistically significant (P = 0.317). There were no cases of mortality in either treatment group (P = 1.000). Adverse drug reactions were reported in two patients (20.0%) receiving azithromycin, whereas no adverse reactions were observed in the doxycycline group, and this difference was statistically significant (P = 0.045). These findings suggest that while both antibiotics were effective in treating scrub typhus without mortality, doxycycline resulted in a shorter fever clearance time and fewer adverse drug reactions compared to azithromycin.

Table 1: Comparison of study groups, by baseline characteristics

		Azithromycin N = 10	Doxycycline N = 10	P value
		n (%)	n (%)	
Age (in years), Mean (SD)		6.7 (3.1)	6.9 (3.0)	0.098
Gender	Male	7 (70.0)	5 (50.0)	0.361
	Female	3 (30.0)	5 (50.0)	
*Statistically significant at p<0.05				

Table 2: Comparison of study groups, by fever clearance time, duration of hospital stay, mortality and adverse drug reactions

		Azithromycin N = 10	Doxycycline N = 10	P value
		n (%)	n (%)	
Fever clearance time (in hours), Mean (SD)		53.1 (2.0)	44.2 (2.1)	0.001*
Duration of hospital stay (in hours), Mean (SD)		46.2 (4.0)	45.2 (4.2)	0.317
Mortality	Yes	0 (0.0)	0 (0.0)	1.000
	No	10 (100.0)	10 (0.0)	
Adverse drug reaction	Yes	2 (20.0)	0 (0.0)	0.045*
	No	8 (80.0)	10 (0.0)	
*Statistically significant at p<0.05				

Discussion

Scrub typhus derives its name from its prevalence in regions with scrub vegetation, which includes sandy, semi-arid, and mountainous desert areas that serve as endemic habitats for the vector.[14] Among the various developmental stages of mites, only the larval stage, known as chiggers, feeds on humans. Consequently, scrub typhus is also referred to as chiggerosis.[15] The classic clinical presentation of scrub typhus includes an eschar at the site of the bite, regional lymphadenopathy, and a maculopapular rash, which is observed in approximately 40–50% of cases. Non-specific manifestations, such as fever, headache, myalgia, cough, and gastrointestinal symptoms, may appear in the early stages of the disease.[16] In rare instances, complications such as encephalitis and interstitial pneumonia may develop in later stages.[17]

In the present study, the majority of patients (12 out of 20; 60%) were male, while the remaining 40% were female. The mean age at presentation was 6.8 years, with an age range of six months to 12 years. Among the 20 study participants, 10 patients received azithromycin, whereas the remaining 10 were treated with doxycycline. The allocation of participants to each treatment group was conducted randomly. A statistically significant difference was observed between the two groups when comparing mean fever clearance time and the incidence of adverse drug reactions. Two patients experienced mild adverse drug reactions: one child reported dizziness, while another developed diarrhoea. However, no statistically significant difference was noted between the groups concerning the mean duration of hospitalization. Furthermore, no patients (0%) died during the study period.

A study conducted by Bal et al.[18] in India in 2019 examined children diagnosed with scrub typhus and reported that doxycycline was the preferred treatment in 85.5% of cases, whereas azithromycin was administered in 14.5%. A meta-analysis conducted by the same authors advocated for the use of azithromycin over doxycycline, particularly in pregnant women and children under eight years of age.[19] Azithromycin, a macrolide antibiotic, is known for its excellent intracellular penetration and prolonged half-life of over 50 hours in pediatric patients, allowing for once-daily dosing and a shorter treatment course. It achieves high intracellular concentrations in neutrophils and macrophages, which are crucial for pathogen phagocytosis. In vitro studies have demonstrated its efficacy against Orientia tsutsugamushi. The mechanism of action of azithromycin involves reversible binding to the 50S subunit of the bacterial ribosome, thereby inhibiting microbial protein synthesis.[20) The most frequently reported adverse effects of azithromycin include mild gastrointestinal disturbances, such as gastric discomfort and abdominal pain.

The present study did not identify any significant differences in gastrointestinal side effects between patients receiving azithromycin and those treated with doxycycline or chloramphenicol. However, the study's small sample size is a limitation, underscoring the need for further research to assess the efficacy of azithromycin in pediatric cases of scrub typhus.[10, 21] Despite its higher cost compared to doxycycline, azithromycin offers comparable efficacy, is easier to administer due to its once-daily dosing schedule and is generally well tolerated with fewer adverse effects. These factors make azithromycin a viable and recommended

treatment option for pediatric patients with scrub typhus.

Conclusion

This study concludes that doxycycline is more effective in achieving fever defervescence and in minimizing adverse drug reactions in patients with scrub typhus. Therefore, doxycycline remains the preferred treatment due to its superior efficacy and safety in pediatric patients with this disease. Further studies with larger sample sizes are recommended to provide a higher level of certainty regarding these findings.

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