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Research Article

Role of Doxycycline in Seropositive Paediatric Dengue and Its Effect on Inflammatory Markers: *A Prospective Randomized Case-Control Study*

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ABSTRACT

Background: Dengue virus (DENV) infection presents a broad clinical spectrum ranging from self-limiting febrile illness to severe dengue driven by systemic immune activation and capillary leakage. Doxycycline possesses immunomodulatory and antiviral properties that may attenuate cytokine-mediated inflammatory cascades.

Objective: To evaluate the effect of oral/intravenous doxycycline on inflammatory markers—erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH), serum ferritin, and serum triglycerides (TG)—as well as routine hematological trends and clinical outcomes in paediatric patients with seropositive dengue.

Methods: An open-label randomized controlled trial was conducted at a tertiary hospital in Karnataka, India, enrolling 70 seropositive paediatric dengue patients (aged 1 month to 14 years) presenting in the febrile phase (days 3–5). Patients were randomized into Intervention (Doxycycline, n = 37, receiving 4 mg/kg/day for 3 days alongside standard WHO care) and Control (Non-Doxycycline, n = 33, receiving standard WHO care). Inflammatory markers and hematological parameters were measured at baseline (Day 0) and post-intervention (Day 4/72 hours).

Results: Baseline demographic characteristics were comparable between groups. No statistically significant differences were observed in median inflammatory marker changes between groups: Ferritin Δ (501 ng/mL vs. 927 ng/mL; p = 0.320), TG Δ (-77 mg/dL vs. -58 mg/dL; p = 0.939), LDH Δ (58 U/L vs. 58 U/L; p = 0.778), CRP Δ (0.2 mg/L vs. 0.75 mg/L; p = 0.292), and ESR Δ (-9 mm/1st hr vs. -7 mm/1st hr; p = 0.439). Clinically, the median hospital fever duration was significantly lower in the Doxycycline group (p = 0.020).

Conclusion: Short-course doxycycline adjunct therapy significantly reduced fever duration in paediatric seropositive dengue patients but did not significantly alter serum concentrations of ESR, CRP, LDH, ferritin, or triglycerides.

Keywords: Paediatric dengue, seropositive dengue, Doxycycline, randomized controlled trial, inflammatory markers, cytokine-mediated inflammation, fever duration, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum ferritin, lactate dehydrogenase (LDH).

Introduction

Dengue is a rapidly expanding mosquito-borne arboviral disease caused by four antigenically distinct serotypes (DENV-1 to DENV-4) belonging to the family Flaviviridae. Primary infection typically induces lifelong serotype-specific protective immunity, whereas secondary heterologous infection carries an elevated risk of severe disease manifestations, such as Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). Paediatric populations are particularly vulnerable to capillary leakage and vascular collapse due to less compliant microvascular beds and reduced physiological reserve.

The pathogenesis of severe dengue is largely driven by host immune activation leading to a hyper-

inflammatory state or 'cytokine storm.' Secondary infection triggers antibody-dependent enhancement (ADE), characterized by cross-reactive non-neutralizing IgG binding to circulating viral particles. This complex promotes elevated viral replication in mononuclear phagocytes, subsequent activation of memory T cells, complement activation, and massive systemic release of pro-inflammatory cytokines including IL-2, IL-6, IL-8, IL-13, IL-18, and TNF-α.

Because no definitive host-targeted antiviral or immunomodulatory therapy is approved for paediatric dengue, clinical management remains strictly supportive. Doxycycline, a synthetic second-generation tetracycline derivative, demonstrates off-target immunomodulatory, anti-inflammatory, and potential antiviral properties. In vitro assays indicate that doxycycline inhibits dengue viral entry and protease activity (NS2B/NS3) while suppressing nuclear factor-kappa B (NF-κB)-mediated transcription of pro-inflammatory cytokines.

Materials and Methods

Study Design and Setting

This single-center, hospital-based, open-label prospective randomized controlled trial was conducted over a 12-month period in Karnataka, India.

Eligibility Criteria

Children aged 1 month to 14 years admitted with acute febrile illness and laboratory evidence of seropositive dengue (NS1 antigen, IgM, or IgG positivity) presenting during the early febrile phase (Days 3 to 5) were eligible for inclusion. Patients with concurrent bacterial co-infections or prior immunosuppressive therapy were excluded.

Interventional Protocol

Enrolled patients were randomized into two arms: Group I (Intervention, n = 37) received standard WHO supportive care plus oral or intravenous doxycycline at 4 mg/kg/day divided every 12 hours for 3 consecutive days (72 hours). Group II (Control, n = 33) received standard WHO supportive care alone.

Results

A total of 70 seropositive paediatric patients were analyzed. Baseline demographic and clinical parameters were well-balanced between groups, with the exception of WHO disease severity classification, which showed a higher proportion of WHO Class II patients in the Doxycycline group

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Table 1: Baseline Demographic and Clinical Characteristics

Demographic Parameter	Doxycycline Group (n=37)	Non-Doxycycline Group (n=33)	Total (N=70)	p-value
Gender, n (%)				0.789
Female	19 (51.4%)	18 (54.5%)	37 (52.9%)	
Male	18 (48.6%)	15 (45.5%)	33 (47.1%)	
Dengue Serotype, n (%)				0.105
Primary (NS1+ / IgM+)	8 (21.6%)	13 (39.4%)	21 (30.0%)	
Secondary (NS1+ / IgG+)	29 (78.4%)	20 (60.6%)	49 (70.0%)	
Mean Age (Years ± SD)	8.32 ± 3.74	7.76 ± 3.65	8.05 ± 3.68	0.524
WHO Severity Class, n (%)				**0.021***
Class I (Without Warning)	9 (24.3%)	13 (39.4%)	22 (31.4%)	

Class II (With Warning)	17 (45.9%)	5 (15.2%)	22 (31.4%)	
Class III (Severe Dengue)	11 (29.7%)	15 (45.5%)	26 (37.1%)	

Table 2: Modulation of Inflammatory Biomarkers (Δ Baseline to Day 4)

Inflammatory Biomarker (Δ)	Doxycycline Group (Median, IQR)	Non-Doxycycline Group (Median, IQR)	p-value
Δ Serum Ferritin (ng/mL)	501.0 (247.4 to 1267.5)	927.0 (188.0 to 1736.5)	0.320
Δ Serum Triglycerides (mg/dL)	-77.0 (-119.5 to -8.5)	-58.0 (-118.5 to 5.0)	0.939
Δ Lactate Dehydrogenase (U/L)	58.0 (-32.5 to 138.5)	58.0 (-47.0 to 207.0)	0.778
Δ C-Reactive Protein (mg/L)	0.20 (-0.97 to 2.68)	0.75 (-0.51 to 3.13)	0.292
Δ ESR (mm/1st hr)	-9.0 (-15.0 to 3.5)	-7.0 (-13.5 to 2.5)	0.439

Discussion

In this prospective clinical trial of paediatric seropositive dengue, short-course doxycycline adjunctive therapy (4 mg/kg/day for 3 days) did not produce statistically significant reductions in serum concentrations of key inflammatory biomarkers (ESR, CRP, LDH, ferritin, or triglycerides) relative to supportive care alone. However, doxycycline administration was associated with a statistically significant reduction in median in-hospital fever duration (1 day vs. 2 days; $p = 0.020$).

This rapid fever defervescence suggests possible local suppression of pyrogenic cytokines, but the lack of changes in system-wide biomarkers or capillary leakage endpoints indicates that short-course oral/IV doxycycline may not halt the broader immunopathological cascade once secondary dengue activation has commenced.

Conclusion

While doxycycline adjunctive therapy accelerates fever resolution in paediatric seropositive dengue, it does not significantly modulate acute-phase inflammatory biomarkers, fluid requirements, or hospital length of stay. Larger randomized trials evaluating direct cytokine profiles and early intervention windows are warranted.

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