ORIGINAL ARTICLE

Role of Doxycycline in Bleeding Manifestations of Dengue Fever

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ABSTRACT

Dengue (pronounced DENgee) fever is a painful, debilitating mosquito-borne disease caused by any one of four closely related dengue viruses. **Aim:** To study effect of doxycycline in bleeding manifestations of dengue fever. **Materials and Methods:** Randomized, double blind, placebo controlled, parallel group study was conducted among 100 seropositive dengue patients, age between 18-60 years (fulfilling inclusion and exclusion criteria) at LLR hospital, Kanpur for Dec 2019 – Oct 2021. These patients were randomized into two groups (50 patients in each). One arm received doxycycline and other was given placebo. **Results:** Patient in case group (on doxycycline) had less bleeding manifestations in comparison to control group (on placebo), only 2% having major bleed as compared to 12% controls, that was statistically significant. But no significant difference seen in terms of minor bleeding. Hemodynamic compromise was more in control group (16%) as compared to treatment group (6%). **Conclusion:** Doxycycline might be having some role in reducing bleeding manifestations in dengue infected patients.

Key words: Dengue , Doxycycline , bleeding manifestations.

Article Information

Received: 01-04-2022

Revised : 23-04-2022

Accepted: 12-05-2022

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INTRODUCTION

Dengue fever is an arthropod-borne viral haemorrhagic fever caused by arbovirus of flavivirus genus having 4 serotypes and concerned vectors like Aedes aegypti and Aedes albopictus mosquitoes. As per estimate of WHO (May 2021) there are an estimated 100-400 million infection each year world-wide. One recent estimate indicates 390 million dengue infections per year (95% credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically (with any severity of disease).[1] Another study, of the prevalence of dengue, estimates that 3.9 billion people, in 128 countries, are at risk of infection with dengue viruses.[2]

Access this article online

Website: www.jcramonline.com

DOI: 10.5530/jcram.2.1.2

Quick Response code

A clinical manifestation ranges from self-limiting fever to profound hemorrhage, shock and death. Dengue fever is described clinically as an acute febrile illness of 2-7 days duration with two or more of the following symptoms headache, rash, retro-orbital pain, myalgia, arthralgia, hemorrhagic tendencies,[3] evidenced by at least one of these i.e (1. A positive torniquet test, 2. Petechiae, ecchymoses, or purpura, 3. Bleeding from mucosa, gastrointestinal tract, injection sites, or other locations, 4. Hematemesis or melena). minor bleeding manifestations are petechiae, purpura, epistaxis and gingival bleeding and major bleeding manifestations includes hematemesis, melena, hematochezia, hemoptysis, and hematuria.

Several studies have been done to evaluate effects of doxycycline on course and outcome of dengue fever.[4-10] Meta-analysis of Jenny Lyn Mangulabnan *et al.*[4] showed that doxycycline helped to lower the serum IL-6 and serum TNF in Day 3 and Day 7 post treatment in dengue fever patients.

There were very few studies conducted on effects of doxycycline in dengue fever in northern India.Thus this study is designed to observe whether doxycycline has any effect in treatment of dengue fever when with other conventional treatment.

METHODS

Randomized, double blind, placebo controlled, parallel group study conducted among 100 seropositive dengue patients, 18-60 years of age (fulfilling inclusion and exclusion criteria) at Lala Lajpat Rai hospital, Kanpur for Dec 2019 – Oct 2021. Selected patients were subjected to history, examination, necessary investigations and then were managed according to National Vector Borne Disease Control Programme (NVBDCP) guidelines. A total of 100 serology proven dengue patients were included and followed up. Two groups (fifty in each) were allocated by simple first and then systematic random sampling. Case group was given doxycycline (100 mg bd for 5 days) and control group was given placebo.

Inclusion Criteria

1. Serology confirmed dengue patients (NS1Ag or IgM Ab or both; by ELISA method)
2. Patient who give written consent to participate in the study
3. Male or non-pregnant, non-lactating female between 18-60 years of age
4. Diagnosis of uncomplicated DF as defined by:
   a) acute febrile illness (axillary ≥ 98.6 or oral ≥ 99.5) with two or more of the following:
      - Headache, Retro-orbital pain, Myalgia, Arthralgia
      - Leukopenia
      - Thrombocytopenia
      - No evidence of plasma leakage

   and
   b) A positive result for dengue infection on NS1 (kit or elisa)
5. Onset of fever less than or equal to 3 days before randomization.

Exclusion Criteria

1. Unwilling patients
2. Patients with associated infection (bacterial/viral/parasitic)
3. Patients with co- morbidities (heart diseases, chronic liver disease, chronic kidney disease etc.)
4. Patients admitted with complications of dengue (hemorrhage, shock, Acute respiratory distress syndrome, plasma leakage).
5. Patients with DF with warning signs and symptoms
6. Patients with afebrile period without use of paracetamol for 24 hr preceding randomization.
7. History of recent (< 120 days of screening) transfusion of platelets or whole blood

Study Technique

- The study was conducted at Post Graduate KPS Institute of medicine GSVM Medical College Kanpur from December 2019 to October 2021. All the patient's fitting inclusion and exclusion criteria were studied that is patient suffering from dengue fever attending medicine OPD, needing admission in medicine department were evaluated for the study. After written informed consent and after history and clinical examination blood samples on the first day, third day and seventh day were drawn for routine complete hemogram, liver function test, renal function test. similarly X Ray chest and ultra-sonography of whole abdomen Electrocardiogram was done on first, third, and seventh day to exclude complications like pleural effusion, ascites or GB edema and any co-morbidities.

Tools of Study

1. Pre-designed proforma with history clinical examination and blood reports with dengue viral serology
2. Automated analyzer for biochemical and pathological test
3. Machine for dengue viral serology.
4. X ray chest machine
5. Ultrasonography machine
6. ECG machine

Observations

100 seropositive dengue patients were included in the study with Male to female ratio being 1.12:1. Age and sex composition between the cases and control group were similar. Majority of cases and control fell in 21-40 years (58%) age group.

Patients in case group in comparison to control group had less bleeding manifestations. 40 (80%) of patients in case group had no bleeding with only 1 (2%) having major bleed as compared to 6 (12%) controls. 34 (68%) had no bleeding in control group. In respect of minor bleeding both groups have no major difference. Hemodynamic compromise was more in control group (16%) as compared to treatment group (6%).)

DISCUSSION

The study was carried out in Post Graduate, KPS institute of Medicine, G.S.V.M. Medical College, Kanpur from December 2019 to October 2021.

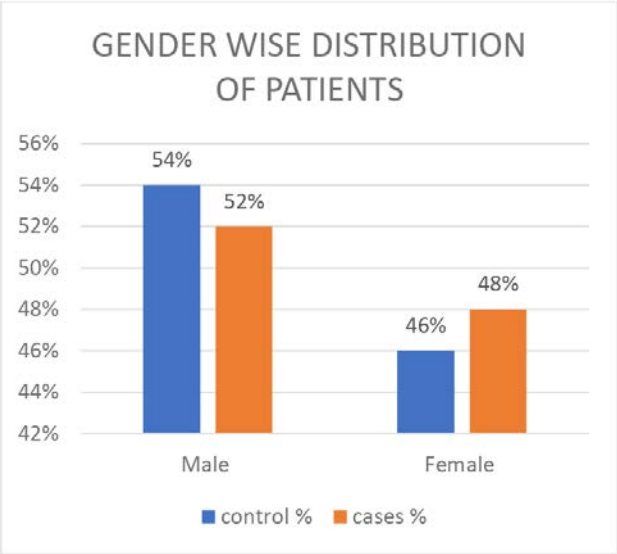

Figure 1: Gender wise distribution of patients.

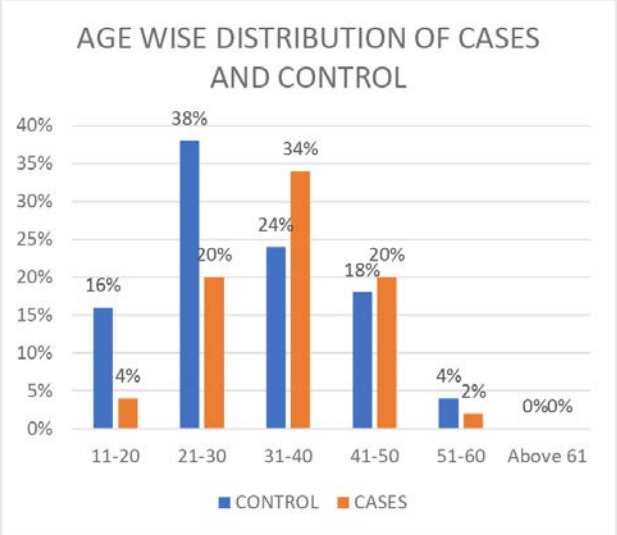

Figure 2: Age wise distribution of cases and control.

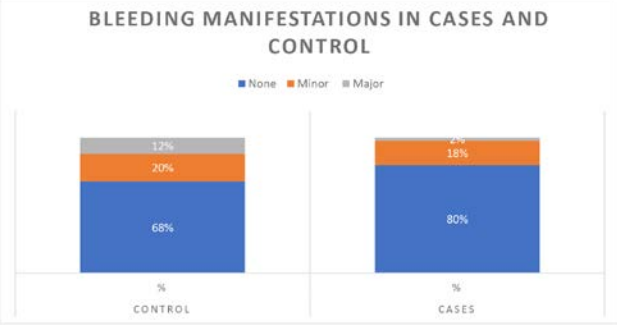

Figure 3: Bleeding Manifestation in Cases and Control.

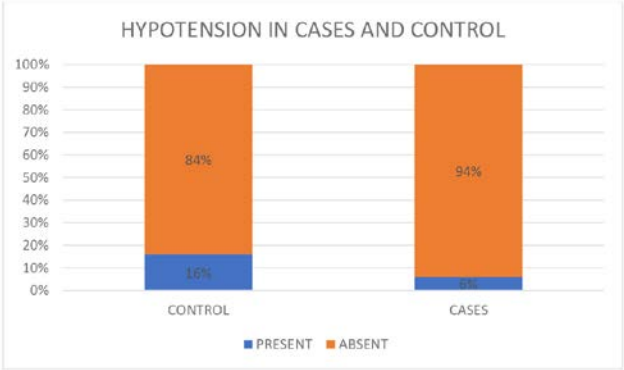

Figure 4: Hypotension in cases and control.

Table 1: Bleeding Manifestation in Cases and Control.

Bleeding	Control		Cases		
	Number	%	Number	%	p value
None	34	68%	40	80%	0.0491
Minor	10	20%	9	18%	
Major	6	12%	1	2%	
Total	50	100%	50	100%	

100 seropositive dengue patients were included in the study and were divided into two groups on the basis of treatment (tablet doxycycline) received by patient or not, 50 patients who received doxycycline were considered as cases and the remaining 50 patients who received placebo pill were considered as control group with Male to female ratio being 1.12:1. Age and sex composition between the cases and control group were similar and was in accordance with Bhattacharjee B *et al.* (2018).[5] Majority of cases and control fell in 21-40 years (58%) age group and comparable with study of Rajesh Deshwal *et al.*[12] which majority of patients fell in 21-40 age group (62.91%).

Patients in case group in comparison to control group had less bleeding manifestations and comparable with study of Bhattacharjee B *et al.* (2018).[11] 80% of patients in case group had no bleeding with only 2% having major bleed as compared to 12% controls. Hemodynamic compromise was more in control group (16%) as compared to treatment group (6%). this finding in accordance with Bhattacharjee B *et al.* (2018).[11]

CONCLUSION

- Major bleeding (epistaxis, melena, hematemesis) was recorded more in patients who did not received doxycycline (Control Group).

- Therefore we concluded that doxycycline might be have potential in decreasing bleeding manifestations in patients of dengue fever.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this Article : Bajpai G, Verma RK. Role of Doxycycline in Bleeding Manifestations of Dengue Fever. J Clinical Res and Appl Med. 2022;2(1):3-6.