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General Medicine

EFFECT OF DOXYCYCLINE ON THROMBOCYTOPENIA AND LEUCOPENIA IN ACUTE DENGUE FEVER PATIENTS

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ABSTRACT **Background:** Dengue fever is a mosquito borne disease commonly associated with leucopoenia and thrombocytopenia. Dengue fever and its complications like bleeding manifestation can be life threatening. This study was conducted to study the effect of doxycycline on thrombocytopenia and leucopoenia in acute dengue fever patients. **Methods:** This case control study was conducted amongst the patients suffering from dengue fever with thrombocytopenia. Cases were dengue patients with thrombocytopenia and leucopenia both. Controls were dengue patients with thrombocytopenia with normal WBC count. An effect of doxycycline was observed on platelet and leukocyte counts at baseline and first, second, fourth, and seventh day in cases and comparison was done. Results: Significant improvement in mean platelet count and leukocyte count was observed in doxycycline group compared to controls (conservative treatment) on day 4th and 7th day of admission. Reduced hospital stay was also seen in doxycycline group. **Conclusion:** The study results indicate that doxycycline is useful modality of treatment to improve leucopenia and thrombocytopenia in dengue patients and to minimize hospital stay.

KEYWORDS :

INTRODUCTION

Dengue is a self limiting acute mosquito transmitted disease characterized by fever, headache, muscle, joint pains, rash, nausea and vomiting. Dengue Fever (DF) is caused by an arbovirus and spread by Aedes mosquitoes. Some infections result in Dengue Haemorrhagic Fever (DHF) and in its severe form Dengue Shock Syndrome (DSS) can threaten the patient's life primarily through increased vascular permeability and shock. Over the past two decades, there has been global increase in the frequency of DF, DHF and its epidemics, with a concomitant increase in disease incidence. According to WHO, there may be 50–100 million dengue infections and half a million dengue hemorrhagic fever (DHF) worldwide every year, with an average case fatality rate of around 5%[1]. . Currently the disease is endemic in all continents except Europe.

Dengue is widespread in India, and outbursts occur every year. Most of the cases are being reported in the monsoon and post-monsoon seasons. All the four serotypes i.e. Dengue 1,2,3 and 4 have been isolated in India.[2] As Aedes aegypti breeding is more common in urban areas the disease was observed mostly prevalent in urban areas. However, the trend is now changing due to socio economic and man made ecological changes, It has resulted in invasion of Ae. aegypti mosquitoes into the rural areas, which has tremendously increased the chances of spread of the disease to rural areas.[2]There is no specific treatment available for dengue viral infection; early detection and supportive care are the most essential aspects of management.

Dengue infection can be prevented in endemic areas by mosquito control, personal protective measures, and vaccination. A number of dengue vaccines are currently under development, while one vaccine, CYD-TDV (dengvaxia), has been licensed for use in a few endemic countries in Latin America and Southeast Asia. There is no direct antiviral therapy available against dengue. Management is supportive primarily consisting of maintaining adequate intravascular volume. The isolation of viral RNA from bone marrow of dengue-infected individuals as well as hypocellularity in bone marrow and inhibition of maturation of megakaryocyte during the primary stage of the disease suggest the suppressive effect of the dengue virus on bone marrow to cause thrombocytopenia.[3,4] Doxycycline is a derivative of tetracycline that possesses broad antimicrobial and anti inflammatory activities. Previous studies have shown that doxycycline inhibits dengue virus plaque formation by disrupting the conformational changes in the viral envelope that are necessary for virus entry.[5-7] Previous studies also found the antidengue properties of doxycycline against all four dengue virus serotypes in vitro.[8-11] The results showed that doxycycline interfered with dengue virus protease and impaired virus binding to the host cells, leading to reduced viral replication in infected cells.

Hence, under the light of above-mentioned data, the present study was undertaken for comparing the efficacy of doxycycline on thrombocytopenia and leukopenia in acute dengue fever patients. Hospital stay and clinical outcome was also observed.

MATERIAL AND METHODS

- Type of study : case control study
- Duration of study : 6 months (June, 2022 to November, 2022)
- Location of study : Smt SCL general hospital (a tertiary health care institute of Gujarat).
- Sample size : 50
- Inclusion criteria : Patients (age 12 years or above) suffering from dengue fever (NS1 antigen and/or IgM positivity by ELISA method) with thrombocytopenia (platelet count <1.5 lakh/cu mm).

Exclusion criteria :

- The patients suffering from other primary/secondary hematological disorders
- Patients using drugs which may impact platelet count and leukocyte count
- Patients needed platelet transfusion or blood transfusion.
- Study protocol :
- Study subjects were divided into controls and cases. The controls were dengue fever patients with thrombocytopenia & normal WBC count (4000–11000/cu mm). The cases were dengue fever

patients with thrombocytopenia with low WBC count (<4000/cu mm).

- The controls were treated conservatively by intravenous fluids in the form of 0.9% normal saline according to requirement along with other symptomatic treatment. The cases were treated with the same treatment as controls with additional oral tablet of doxycycline 100 mg BD for 5 days
- All patients of cases and controls were observed for platelet counts and total leukocyte counts at baseline(day 0), day 1, 2, 4, and 7 of admission. Improvement of platelet and leukocyte count, duration of hospital stay, and clinical outcome were observed and compared by statistical analysis between the controls and cases groups to see the effect of doxycycline on thrombocytopenia and leucopenia.
- The comparison between controls and case groups was done by ANOVA test, and $P < 0.05$ was considered as significant difference.

RESULTS

The present study included 50 indoor dengue fever patients having thrombocytopenia. The mean age of dengue patient was 33.5 ± 12.4 years and male:female ratio was 3:2. Out of 50 thrombocytopenic dengue patients, 23 patients had normal leukocyte were considered as controls and 27 patients had leucopenia were considered as cases.[Table 1]

The controls were treated with conservative management of intravenous fluid and symptomatic treatment. The cases were treated with doxycycline Mean platelet count in controls and cases was observed at baseline and first, second, fourth, and seventh day of admission [Table 2] and compared with each other. [Table 3]

No significant difference was there on comparison of the mean platelet count on first day and second day in between controls and case groups. However, there was significant improvement of mean platelet count at fourth and seventh day in cases compared to control. [Table 3]

Mean leukocyte count in controls and cases was also observed at baseline and first, second,

Table 1: Distribution of patients among cases groups according to treatment

Cases group	Number of patients	Percentage
Doxycycline group	27	54
Controls	23	46
Total	50	100

fourth, and seventh day of admission [Table 4] and compared with each other [Table 5].

No significant difference was there on comparison of the mean total leukocyte count on first day and second day in between controls and case groups. However, there was significant

Table 2: Day wise distribution of mean platelet count among different study groups

Group	Baseline		1st Day		2nd Day		4th Day		7th Day	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Controls	65,600	19,912.60	73,100	21,518.13	87,400	22,906.27	98,000	150 14.57	1,34,700	21837.56
Cases (Doxycycline group)	58,800	13,281.19	75,300	12,107.12	92,350	10,403.35	1,12,500	116 61.97	162,800	29229.32

Table 3: Comparison of day wise mean platelet count between controls and cases groups

	Follow-up				
	Baseline	1st Day	2nd Day	4th Day	7th Day
Controls versus Cases (Doxycycline group)	0.1566	0.6519	0.3182	0.00036*	0.00042*
*Significant P value					

improvement of mean total leukocyte count at fourth and seventh day in cases. [Table 5]

Mean duration of hospital stay was compared between cases and control groups [table 6].

Table 4: Day wise distribution of mean total leukocyte count among different study groups

Group	Baseline		1st Day		2nd Day		4th Day		7th Day	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Controls	5300	590.07	5830	663.24	6640	728.47	7580	723.26	7880	1285.77
Cases (Doxycycline group)	3200	364.78	5750	917.64	6920	719.34	8440	1233.24	8800	930.72

Table 5: Comparison of day wise mean total leukocyte count between controls and cases groups

Group Versus Group	Follow-up				
	Baseline	1st Day	2nd Day	4th Day	7th Day
Controls versus Cases (Doxycycline group)	0.00*	0.7296	0.1789	0.0050*	0.0025*
*Significant P value					

There was significant difference in mean duration of hospital stay between cases and controls. [Table 7] No mortality was observed among cases and controls, all patients discharged were in stable condition and in the symptom free state.

Table 6 : Mean duration of hospital stay in cases vs control

Group	Mean	SD
Controls	8.7	1.25
Cases (Doxycycline group)	7.2	1.28

Table 7 : Comparison of mean duration of hospital stay between controls and cases groups

Comparison of mean hospital stay in days	P
Controls versus Doxycycline group (8.7 vs 7.2 days)	0.00*
*: Significant	

DISCUSSION

The present study was undertaken for comparing the efficacy of doxycycline on thrombocytopenia and leukopenia in acute dengue fever patients.

In current study, the mean age of dengue patient was 33.5 ± 12.4 years, and the male to female ratio was 3:2. AL-Samadi MM et al.[12] reported that the mean age of the dengue patients was 25.32 years and 54% of the patients were male. In an another study conducted by Sathyapalan DT et al.[13] the mean age of the patients was 51 years and 73% of the patients were males. Patel K et al.[14] reported that 67% of the patients were males. A comparison of the studies shows that young patients are more involved with male predominance. The lower occurrence of dengue in old age and females should be evaluated on genetic, pathological, and social basis in further studies.

In the current study, significant improvement was seen in respect to the mean platelet count and mean leukocyte count on fourth and seventh day of hospital admission in patients treated with doxycycline (cases) in comparison of the control group. Non significant results were obtained while comparing the mean platelet count at first day and at second day in between the control group and doxycycline group.

Our results were in concordance with the results obtained by Mangulabnan JL et al.[15] who also reported similar findings. Their study assessed the effect of doxycycline on lowering interleukin 6 (IL-6) and tumor necrosis factor (TNF) among patients with DHF. In the pooled analysis using standardized paired difference in mean, doxycycline was favored in lowering the serum IL-6 and serum TNF, both in third and seventh day post treatment with a P value of <0.00001. Their study showed that doxycycline lowered the levels of serum IL-6 and TNF, and cytokines were directly implicated in the severe type of dengue.

Rothan HA et al.[16] determined the potential activity of doxycycline against dengue virus replication in vitro. They concluded that the doxycycline significantly inhibited viral entry and postinfection replication of dengue, with serotype-specific inhibition.

Another study conducted by Fredeking TM determined the effect of

doxycycline treatment on cytokine levels, including TNF and interleukin 6 (IL-6) along with mortality in dengue patients at high risk of complication. In their study, 231 DHF patients were randomized to receive either standard supportive care or supportive care in addition to oral doxycycline twice daily for 7 days. Their findings suggested that doxycycline can provide a clinical benefit to dengue patients at high risk of complications.[17]

An additional potential benefit to using doxycycline in the treatment of dengue fever or DHF is its recently discovered ability to inhibit dengue virus multiplication in tissue culture. Doxycycline, but not tetracycline, was able to interact with the dengue virus E protein to inhibit a conformational change, which is an essential step in the process by which the virus enters susceptible cells. The study indicates that doxycycline may provide a clinical benefit in the treatment of dengue virus infection by modulating the cytokine cascade.[18] In the current study, mean length of hospital stay was more in the control group (8.7 days) compared to cases(doxycycline group - 7.2 days), and statistically significant results were there on comparison. Mortality was absent in all dengue patients. Our results were in concordance with the results obtained by Sathyapalan DT et al.[13] who reported the absence of mortality among acute dengue fever patients.

CONCLUSION

Under the light of above-obtained data, conclusion can be withdrawn that the treatment with doxycycline significantly shows better and faster positive outcome in dengue patients in form of improving platelet and leukocyte count. Their use may also reduce related complications, morbidity, hospital stay, and financial burden. The study recommends their inclusion in treatment guidelines of dengue. Further studies are needed to understand their synergetic or additive effect.

REFERENCES

1. WHO. Dengue and Dengue Haemorrhagic Fever. Factsheet No 117, Revised May 2008. Available from: http://www.who.int/mediacentre/factsheets/fs117/en/.
2. https://nvbdcp.gov.in/Doc/Clinical Guidelines.pdf
3. Singh M, Chakraborty A, Kumar S, Kumar A. The epidemiology of dengue viral infection in developing countries: A systematic review. J Health Res Rev 2017;4:104-7
4. Henchal EA, Putnak JR. The dengue viruses. Clin Microbiol Rev 1990;3:376-96.
5. Wilcox JR, Covington DS, Paez N. Doxycycline as a modulator of inflammation in chronic wounds. Wounds 2012;24:339– 49
6. AL-Samadi MM, Ali KS. Evaluation of some hematological and serological changes in dengue patients of Lahj-Yemen. Electronic J University Aden Basic Appl Sci 2020;1:25-9.
7. Sathyapalan DT, Padmanabhan A, Moni M, P-Prabhu B, Prasanna P, Balachandran S, et al. Efficacy & safety of Carica papaya leaf extract (CPLE) in severe thrombocytopenia (≤30,000/µl) in adult dengue – Results of a pilot study. PLoS one 2020;15:86-99.
8. Orellana MA, Gomez-Lus ML. Which is the best empirical treatment in patients with urethritis? Rev Esp Quimioter 2011;24:136–42
9. Polat KY, Tosun MS, Ertekin V, Aydinli B, Emre S. Brucella infection with pancytopenia after pediatric liver transplantation. Transpl Infect Dis 2012;14:326–9
10. Skulason S, Holbrook WP, Thormar H, Gunnarsson GB, Kristmundsdottir T. A study of the clinical activity of a gel combining monocaprin and doxycycline: A novel treatment for herpes labialis. J Oral Pathol Med 2012;41:61–7.
11. Wilcox JR, Covington DS, Paez N. Doxycycline as a modulator of inflammation in chronic wounds. Wounds 2012;24:33949.
12. AL-Samadi MM, Ali KS. Evaluation of some hematological and serological changes in dengue patients of Lahj-Yemen. Electronic J University Aden Basic Appl Sci 2020;1:25-9.
13. Sathyapalan DT, Padmanabhan A, Moni M, P-Prabhu B, Prasanna P, Balachandran S, et al. Efficacy & safety Journal of Family Medicine and Primary Care of Carica papaya leaf extract (CPLE) in severe thrombocytopenia (≤30,000/µl) in adult dengue – Results of a pilot study. PLoS one 2020;15:86-99.
14. Patel K, Patel D, Das VK. Hematological parameters and its utility in dengue fever: A prospective study. Int J Sci Res 2016;1077-9.
15. Mangulabnan JL, Ogbac F. Effects of doxycycline on lowering IL-6 and TNF among patients with dengue haemorrhagic fever: A meta-analysis. J Infect Dis Ther 2017;5:71.
16. Rothan HA, Buckle MJ, Ammar YA, Mohammadjavad P, Shatrah O, Noorsaadah AR, et al. Study the antiviral activity of some derivatives of tetracycline and non-steroid anti-inflammatory drugs towards dengue virus. Trop Biomed 2013;30:681-90.
17. Fredeking TM, Zavala-Castro JE, González-Martínez P, Moguel-Rodriguez W, Sanchez EC, Foster MJ, et al. Dengue patients treated with doxycycline showed lower mortality associated to a reduction in IL-6 and TNF levels. Recent Pat Antiinfect Drug Discov 2015;10:51-8.
18. Yang JM, Chen YF, Tu YY, Yen KR, Yang YL. Combinatorial computational approaches to identify tetracycline derivatives as flavivirus inhibitors. PLoS One 2007;2:e428.