



TO STUDY THE ROLE OF CARICA PAPAYA LEAF EXTRACT CAPSULES IN DENGUE INDUCED THROMBOCYTOPENIA IN TERTIARY CARE HOSPITAL IN ROHILKHAND REGION

Clinical Research

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ABSTRACT

Dengue is a viral disease which is rapidly expanding health problem in over 125 countries and is responsible for a sizable number of deaths. Approximately 2.5 billion people lives in dengue-risk region with about 100 million new cases each year worldwide. There is no anti-viral chemotherapy or vaccine for dengue virus and the management of dengue virus infection is essentially supportive and symptomatic. The decline in platelet count leads to complications and mortality. This study was conducted to evaluate the role of carica papaya leaf extract in patient with dengue fever.

Aim: The administration of carica papaya leaf extract in patient of dengue fever and to look for increase in platelet counts in patient of dengue fever associated with thrombocytopenia.

Material and Method: Serologically confirmed 100 cases of dengue fever who were hospitalized were included in this study. It is an open-labeled randomized controlled trial was carried out. The subjects were divided into two groups, as control and intervention group. Both were managed by standard management guideline for dengue fever. In addition to this intervention group received carica papaya extract leaf tablets (1100mg) twice daily for four days. All of them were followed daily with platelet count monitoring.

Results: The results indicated that carica papaya leaf extract tablets had shown significant increase ($p < 0.001$) in platelet count over the therapy duration, in dengue fever patients, confirming carica papaya leaf extract tablets accelerates the increase in platelet count and also prevent the complications compared to control group.

Conclusion: Thus this study concluded that carica papaya leaf extract does significantly increase the platelet count in patient with thrombocytopenia associated with dengue fever.

KEYWORDS

Dengue, Thrombocytopenia, carica papaya leaf extract.

INTRODUCTION

Dengue is a viral disease transmitted by the bite of the Aedes mosquito, has reached alarming proportion in past few years. Dengue is prevalent in tropical and sub-tropical regions around the world. Today endemic in more than 12 countries and infecting nearly 50-270 million people every year¹. Travelers from non-endemic areas to dengue endemic/affected areas are also exposed to the possibility of infection². This makes it an international public health concern, affecting individuals from countries even when the disease is not prevalent.

The geographic region at risk for dengue has increased fourfold over the past three decades, unprecedented for a vector-borne disease³. Dengue virus (DENV) is an arthropod-borne flavivirus associated with both hemorrhagic fever and hemorrhagic shock⁴.

Pathology

Many cases of dengue are asymptomatic, especially in children and in adults with a first infection. In other cases it may appear as self-limiting undifferentiated fever or classic dengue fever². An incubation period varying from 3 to 14 days is followed by a febrile illness consisting of sudden onset of fever, headache, myalgia, arthralgia, rash and hemorrhagic manifestations. The DENV hemorrhagic fever is characterized by fluid leakage into interstitium⁵. A number of atypical manifestations have also been reported in the literature, which includes encephalitis, encephalopathy, myocarditis, hepatitis and cholecystitis⁶.

The mechanism behind the platelet reduction is not yet clear till date due to lack of suitable animal model studies⁷. There are two mechanisms causing thrombocytopenia. DENV induced bone marrow suppression decreases the platelet synthesis and leads to thrombocytopenia⁸. Immune-mediated clearance of platelets also causes thrombocytopenia⁷⁻⁸. In this mechanism anti-platelet antibodies clears the virus attached platelets via complement activation and also inhibits ADP- induced platelet aggregation⁷⁻¹².

Management of Dengue Fever

Treatment for dengue is usually symptomatic. Some cases require

platelet transfusion and fluid management². One of the most disturbing aspect of the problem of dengue is that there is no specific effective antiviral agents available to treat dengue. A study demonstrated the possible effectiveness of cocktail extract prepared from four species of phyllanthus against the DENV¹³.

Attempts to develop an antiviral for dengue has met several hurdles. Dengue is caused by four distinct serotype which often undergo mutation¹⁴. Like in other ribonucleic acid (RNA) viruses, these mutations are due to error-prone of quasispecies. It is currently unclear which viral genome results in a higher viral titre¹⁵. An antiviral would have to be effective against all the serotype¹⁶.

Use of Papaya Plant in Medicine

The papaya plant or C. papaya has been used since ancient times for the treatment of a number of disease conditions. Various beneficial effects of extract from the leaves, fruit and seeds have been suggested through scientific studies. The chymopapain and papain extract of the leaves are useful in the treatment of digestive disorders. The extracts from the fruits and seeds have bactericidal properties¹⁷.

Possible Mechanism of Action of Papaya Extract in Dengue

The papaya plant possibly brings about its effect in dengue by treating the thrombocytopenia associated with the condition. A study has reported membrane stabilizing properties of c.papaya L. extracts in in vitro studies. The study found that c.papaya L. extracts inhibited heat-induced and hypotonicity-induced hemolysis of erythrocytes obtained from both healthy individuals and individuals with dengue infection; the effect was observed at the lower concentration of extract.

AIM AND OBJECTIVE

The administration of carica papaya leaf extract in patient of dengue fever and to look for increase in platelet counts in patient of dengue fever associated with thrombocytopenia.

MATERIALS AND METHOD

An open labeled Randomized controlled, Prospective study was conducted at a tertiary care hospital SRMS-Institute of Medical

Sciences Hospital, Bareilly in Rohilkhand region to evaluate the efficacy and safety of carica papaya leaf extract, for thrombocytopenia associated with dengue fever.

The subjects were randomized into two groups, as control and intervention group. Both the groups were managed by the standard management guideline for dengue except steroid administration. In addition to this, the intervention group received CPLE tablet three times daily for 4 days. All of them were followed daily with platelet monitoring.

Patient fulfilling the following inclusion criteria were taken up for the study from 2016-2017.

Inclusion criteria

1. Male and female patients who were confirmed to have dengue fever either by NS1 antigen or IgM positive report.
2. Patients with platelet count less than or equal to 100,000/micro liter.

Exclusion criteria

1. Patient with dengue hemorrhagic fever.
2. Pregnant and lactating women.
3. Patient who received blood or blood products during the current illness.
4. Patient with impaired renal and liver profiles.

All the patients who were included in this study were managed with the standard protocol/guideline therapy for dengue fever. In addition to the standard management protocol, after randomization in two groups, the study/intervention group received CPLE 1100 mg per orally three times in a day for 4 days and the controlled group received placebo for same duration and they were followed daily with platelet counts.

RESULTS

All the 100 subjects enrolled were diagnosed as dengue cases either by NS1 antigen test or by IgM positive status for dengue.

TABLE NO 1: Sex distribution between intervention and control group

GENDER	INTERVENTION	CONTROL	TOTAL
MALE	34	36	70
FEMAL	16	14	30
TOTAL	50	50	100

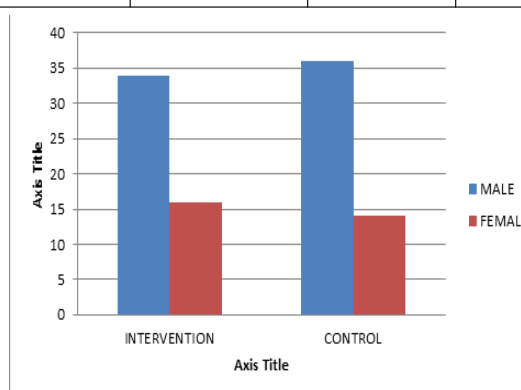


Fig 1: Sex distribution between intervention and control group

TABLE NO 2: Age distribution between intervention and control groups

AGE(yrs)	INTERVENTION	CONTROL
15-24	5	14
25-34	9	5
35-44	13	9
45-54	8	8
55-64	10	12
65-74	5	2
TOTAL	50	50

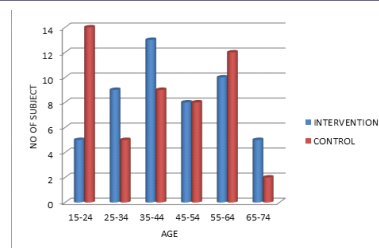


Fig 2: Age distribution between intervention and control groups

TABLE NO 3: platelet minimum, maximum and median values for both the group

DAYS	CONTROL (n=50)			INTERVENTION (n=50)			P VALUE
	MINI MUM	MAXIM UM	MEDI AN	MINIM UM	MAXIM UM	MEDI AN	
DAY1	10000	110000	44000	16000	109000	41500	0.735
DAY2	12000	87000	38000	21000	130000	50000	0.015
DAY3	7000	90000	36500	13000	1450000	60500	<0.001
DAY4	7000	120000	41000	5000	1760000	83000	<0.001

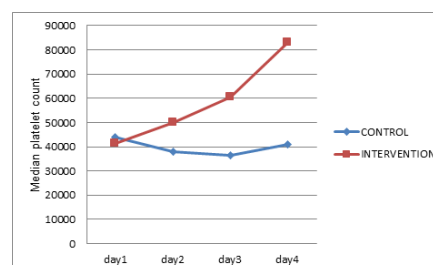


Fig 3: comparison of platelet count between two groups during different time point

1.1 Demographic characteristics: distribution of sex of the subjects in both the groups did not show any difference (table 1), men were more than women most patient infected were in age group of 35-44 & 55-64 yrs old and the distribution in both the groups did not show any difference (table2).

1.2 Primary outcome variables: in this study, platelet count was considered as the primary outcome. Non parametric test- Friedman's test was used to compare difference between both the groups also minimum, maximum and median values are also presented (table 3).

Above data reveals that at day 1 the median platelet count was 41.50 in intervention group, which was comparable with 44.50 in control group and the difference was not significant.

After the treatment at the end of day 4, the median platelet count showed a significant increase in the intervention group when compared to control group as compared to baseline value ($p < 0.001$).

DISCUSSION

Dengue infection is a wide clinical spectrum ranging from self limiting to life threatening conditions. Thrombocytopenia is one of the associated conditions that can lead to dengue hemorrhagic fever and aggravating shock leading to mortality. Despite of its complex manifestations, the management is relatively simple and inexpensive but requires a prudent approach.

In this study we observed a significant increase in platelet counts in the intervention group. It is demonstrable that the subjects in the intervention group that received CPLE and can reach faster and higher increase in platelet counts as compared to control group from baseline value also this prevent dengue fever patient to further develop dengue hemorrhagic fever.

CPLE is shown to increase the expression of Arachidonate 12-lipoxygenase (ALOX12) and Platelet-Activating Factor Receptor (PTAFR) gene responsible for platelet production by FC=15 and FC=13.42 respectively¹⁴.

CONCLUSION

This study showed significant rise in platelet counts much faster and higher in subjects who received CPLE (1100mg) in patient of thrombocytopenia associated with dengue fever.

Fall in platelet counts is one of the concerns in dengue cases, this novel option of CPLE can be optimum offering which is simple, convenient, cost effective, efficacious and safe in patient of dengue fever associated with thrombocytopenia.

LIMITATION

Patient with dengue hemorrhagic fever were excluded from this study, so the efficacy in these patient of CPLE could not be evaluated for which further studies are recommended.

Patients who were undergoing blood and blood product comparative study should be conducted to evaluate its efficacy to bring down the transfusion volume and the rates.

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