ORIGINAL ARTICLE

Role of carica Papaya Leaf Product in Improving the Platelet Count in Patients with Dengue Fever

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ABSTRACT

BACKGROUND: Dengue is one of the most important arthropod-borne viral infection of humans in terms of both illness and death. Millions of people are vulnerable to dengue(Estimated 50-100 million per year).Dengue is caused by Dengue virus(DENV)1-4 through AedesAegyptimosquitoe as the predominant vector. It is important torecognise and differentiate the clinical signs and symptoms, alterations in the laboratory parameters in Dengue Fever. Decrease in platelet count is an important finding that develops later after the febrile episode. The treatment of Dengue feveris mainly supportive and symptomatic. No specific treatment is available for dengue associated thrombocytopenia. In several Asian countries Carica Papaya has been used extensively for improving platelet count **AIM:** To evaluate the effect of carica papaya leaf extract on platelet count in patients of dengue fever with thrombocytopenia. **METHODS:** 100 cases of confirmed dengue infection were studied. The subjects were randomized in to two groups,control and study group. Cases were followed-up daily for the clinical and laboratory parameters.They were managed according to the standard guidelines. Study group received Carica papaya leaf extract 500mg three times daily for five days and control group received placebo capsules in same frequency. Platelet count of both the groups were monitored daily and compared. **RESULTS:**The result showed that there was a significant increase (p<0.01) in platelet count in study group as compared to the control group. Thrombocytopenia associated complications were minimal in study group than the control group. Need for platelet transfusion was less in study group than control group. **CONCLUSION:** The study concluded that use of Carica papaya leaf extract in patients with thrombocytopenia has improved the platelet count significantly and helped in preventing the complications associated with thrombocytopenia.

Key Words: Carica papaya, Dengue fever, Thrombocytopenia, Bleeding manifestations

INTRODUCTION

Dengue is the most important viral infection transmitted by mosquitoes to humans in terms of both illness and death.[1] Outbreaks of dengue fever have been reported quite frequently from different parts of the country. According to WHO report, the mortality in untreated cases of Dengue Fever was reported to be as high as 20%, while the hospitalized patients had a mortality rate of less than 1%.[2]

Dengue is Caused by asingle stranded RNA virus belonging to the Flavivirus group possesses antigens that overlaps with yellow fever, Japanese encephalitis &

West Nile fever viruses. ItComprises of four closely related yet serologically distinct viruses called DEN-1, DEN-2, DEN-3, DEN-4.It is the most prevalent flavivirus with an estimated 50-100 million infection and 200000-500000 cases of haemorrhagic fever throughout the tropical regions of the world depending upon the epidemic activities.[2,3] Dengue viruses are transmitted to humans through bite of Infected female AedesAegypti mosquitoes.Once infected, a mosquito remains infected for life transmitting viruses to susceptible individuals during probing and feeding.
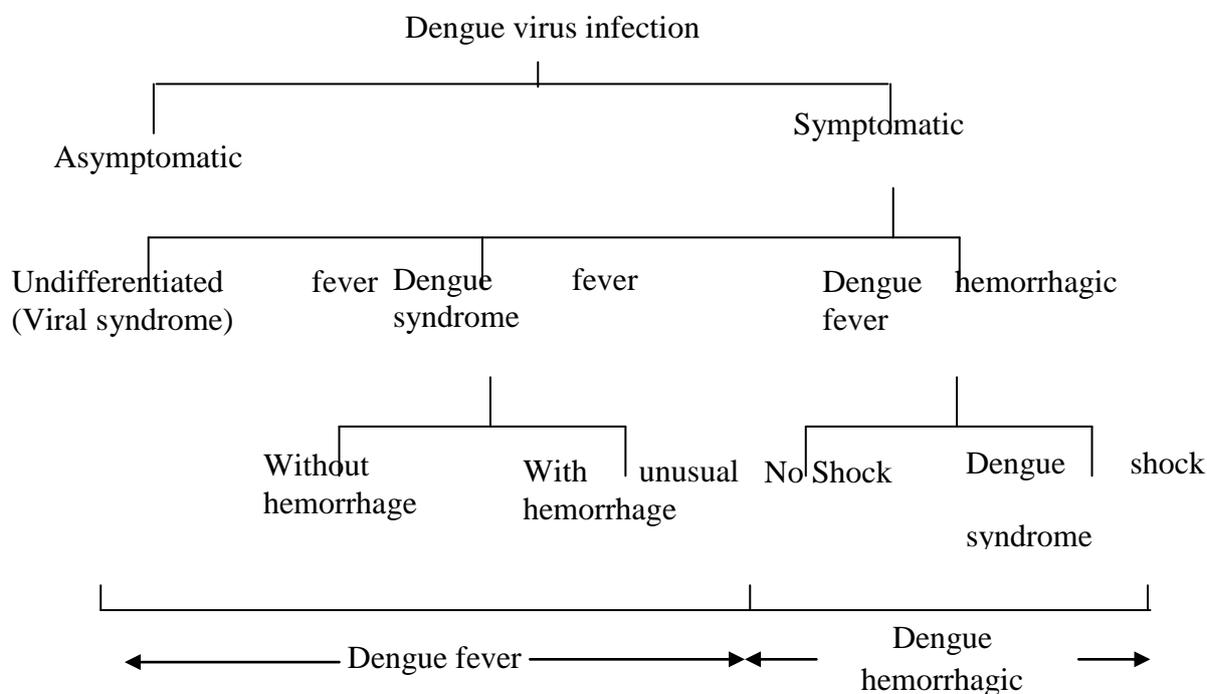
CLINICAL MANIFESTATIONS OF DENGUE

Symptoms of dengue begins usually after 3 to 6 days after the mosquito bite and it can last up to 10 days. Initial presentation is acute febrile illness with fever, myalgias, chills, headache etc. Later if untreated, it progresses to Dengue Hemorrhagic Fever (DHF) with capillary

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leakage and bleeding manifestations. At this stage if patients do not receive intravenous fluid resuscitation ,it progresses to Dengue Shock Syndrome(DSS) and death of a patient.[4,5] Thrombocytopenia is the characteristic finding in patients with dengue.The mechanism of thrombocytopenia is not clear but proposed mechanisms are 1.DENV induced bone marrow suppression.[4] 2.Immune mediated clearance of platelets from circulation.[4,5]The treatment of Dengue fever is mainly supportive and symptomatic.[1,6,7] No proven specific vaccine or drug is available for treatment of dengue and associated thrombocytopenia. In several Asian countries Carica Papaya Leaf Extract (CPLE) has been used extensively for improving platelet count. CPLE contains many active components like papaine, chymopapaine, cystatine, tocopherol, ascorbic acid, glucocynoolates etc.They are related with anti inflammatory, anti tumour activity, and immunomodulator activity.[8,9]It has been hypothesized that increase in activity of certain genes likeArachidonate 12-lipoxygenase(ALOX-12),Platelet –Activating Factor Receptor (PTAFR) have been shown to influence platelet production and platelet aggregation.[10]Several studies are done to determine the usefulness of herbal medicines in treatment of dengue. This study has been undertaken to evaluate the effect of Carica papaya leaf extract on platelet count in patients of dengue fever with thrombocytopenia.

Dengue virus infection

Asymptomatic

Symptomatic

Undifferentiated fever (Viral syndrome)

Dengue fever syndrome

Dengue hemorrhagic fever

Without hemorrhage

With unusual hemorrhage

No Shock

Dengue shock syndrome

← Dengue fever → ← Dengue hemorrhagic →

MATERIAL ANDMETHODS
Source of Data: All the adult patients with suspected DengueFever admitted to medical wards in ESIC Medical college hospital,Gulbarga.

Method of collection of data: The data for this study was collected bypatient evaluation which was done by detailed historytaking, clinical examination and relevant investigations.Informed consent was taken from all subjects.

Sample size : 100

Study design : A double blind ,randomized prospective clinical study

Inclusion criteria: All the adult patients with Clinical featuressuggestive of Dengue infection, later on confirmed byserology were included in this study.

Exclusion criteria: Dengue fever with any other identifiedspecific infection, Dengue hemorrhagic fever grade III/IV, pregnant and lactating women, patients with Immune Thrombocytopenic Purpura, hemophilia, leukemia were excluded from the study.

Methodology: 156 patients, identified as probable cases byclinical suspicion, admitted to medical wards in ESIC

Medical College Hospital, Gulbarga,were registered in the study. The case definition wasbased on compatible history and examination based onWHO criteria, confirmed by Dengue serology. Adetailed demographic data, clinical history, physicalexamination and relevant baseline investigations weredone.For all cases, the rapid IgM and IgG capture ELISAtest (MRL diagnostics), which has become the goldstandard for the serological diagnosis of dengue feverwas done. Serum samples were obtained on an averageof 5 to 7 days after DF symptoms had appeared. The number of cases included in the study,based on the above criteria, was 100.The subjects were randomized in to two groups,50 each, as Control and Study group.The cases werefollowed-up daily for the clinical and laboratory parameters mainly platelet count till their discharge from the hospital. The patients were treated with IV fluids,paracetamol, antacids, platelet transfusion and inotropics asper WHO criteria for treatment of dengue.In addition to this, study group received Carica Papaya Leaf Extract (CPLE) capsules 500mg three times a day and control group received placebo capsules in same frequency.Caseswere stratified based on the presence or absence ofcomplications like shock and haemorrhage in to variousdengue types. The frequency of various signs andsymptoms and the values of laboratory tests werecompared.

Investigations: The Study requires thefollowing investigations

- Complete haemogram
- Liver function test (LFT)
- Renal function test (RFT)
- Chest Xray
- Ultrasound abdomen
- Coagulation profile
- ECG
- Dengue antibodies– Ig M &Ig G by CaptureELISA

Statistical analysis: The collective data as well as the proportionsand percentages of variables are projected byappropriate charts, tables and graphs. The platelet count, average duration of hospital stay, requirement of platelet transfusion in both control and study groups were compared statistically by student t-test.

RESULTS

All the 100 cases were diagnosed as dengue cases by standard test. The study was carried out on 100 patients out of which 50 patients as study group received CPLE and 50 patients as control group received placebo capsules. There were no severe adverse eventswith CPLE except GI disturbances like nausea, vomiting which were seen in both the groups supporting the tolerability and safety of CPLE. None of the subjects were discontinued the treatment because of any adverse events.

Mean age of the patients was 36 years. Maximum numbers of patients were in the age group of 21-30 years and minimum were in the agegroup of 60 and more years. Patients below the age of15 years and above 65 years were excluded from the study. There were 55% females and 45% males. Age and sex matching was done in both study and control group.

Most common presenting features were fever(100%) followed by myalgia (82.5%), headache (75%),fatigue (55%), arthralgia (55%). Least commonpresenting features were malena (2.5%) and seizure(2.5%).

45% of the patients are positive for IgM antidengue antibodies and 55% are positive for both IgMand IgG antibodies. This indicates that secondarydengue infection was more compared to the primary dengue infection. Dengue IgGAb positivity appears tobe a bad prognostic indicator. The titres of theantibodies were high in patients with secondary dengueinfection and in those with severe disease.

Table 1: Dengue antibody positivity

Dengue antibody	No. of patients	Percentage (%)
IgM	45	45.00
IgM&IgG	55	55.00

In this study, platelet count was considered as primary outcome variable whereas RBC count, WBC count and Hematocrit were secondary end points. Mean platelet count was 57000/cmm. Thebleeding manifestations were not very well correlated with the platelet count.

Table 2.Average platelet count (in Thousands)

	Control group	Study group
Day 1	60	59
Day 2	56	55
Day 3	54	72
Day 4	66	89
Day 5	75	98
Day 6	98	110
Day 7	132	140

Average plateletcount at the time of discharge was 132000 in control group and 140000 in study group.Our study showed that there was a significant increase in platelet count as compared to control group. On first day platelet count of study group was 59.02+/-18.63 thousands,95% CI +/-2.58 and platelet count of control group was 59.92+/-18.63 thosands,95% CI +/-2.58.Difference was not significant (p value 0.30).There was a significant increase in platelet counts in study group on day3,day4 and on day 5 as compared to control group which was statistically significant (p<0.01).

We followed platelet transfusion criteria as per WHO. Total number of patients required platelet transfusion was 37. Out of total 50 study patients,only 14(28%)patients required platelet transfusion while in control group, 23(46%) patients required platelet transfusion.It was observed that average platelet transfusion requirement of study group was significantly less compared to control group(p <0.01).

On first day of admission, evidence of hemoconcentration as indicated byraised Hb% (>16gm%) and HCT(>45%) was seen in22.5% and 20% of the patients in study and control group respectively. At the time of discharge, with normalization of these parameters, there was no significant difference in the hematocrit values in both groups.The difference in RBC count in both groups at admission and at the end of the treatment was not statistically significant.There was a significant increase in WBC count after 4th day onwards in study group as compared to control group. It can be correlated to the declining viraemia at this point of time.

The average hospitalization period in control group was 6.42+/-0.98 days, while in study group it was 3.45+/-0.98 days.Statistical analysis showed significant difference(p<0.01). Patients in study group were discharged early compared to the patients in control group.

DISCUSSION

Dengue is one of the important viral infections with high morbidity and increased chances life threatening complications if not recognized in early stages of the disease.Thrombocytopenia is a characteristic finding in dengue fever and has more concern.A study conducted by Schexneideret al[11] found that platelet count does not correlate well with the clinical bleeding. Patients should be monitored closely for hemorrhagic manifestations and symptomatic thrombocytopenia may require platelet transfusion.

With respect to clinical features in our study , similar results were observed in a study conducted byAgarwal A, Chandra J et al.[12], Kabra SK et al.[13] where fever, myalgias , headaches were predominant symptoms.Similar results were observed in a studyconducted by G.N. Malavige et al in Sri lanka[14],where fever was found in 100%, myalgia in 78.5%,headache in 78% and arthralgia in 56.7%.

In this study, there was a significant improvement in platelet count in study group as compared to control group. Thrombocytopenia associated complications,hemorrhagic manifestations and need for platelet transfusion were less in study group as compared to control group.This indicates the positive and beneficial role of CPLE in Dengue fever with thrombocytopenia.It is similar to a study conducted by Sathasivam et al .(2009), Gowda et al[15]and Subentiran et al.[10] A recent trial from Malaysia showed significant increase in platelet count after 40-48 hours of first dose of papaya leaves juice.

Thebleeding manifestations were not very well correlatedwith the platelet count. Similar results were observed ina study conducted by S.Sharmaet al[16] during an outbreakof dengue fever in Delhi in 1996.

Additionally there was a significant increase in WBC count after 4th day onwards in study group as compared to

control group. It can be correlated to the declining viraemia at this point of time.CPLE may have stimulating action on myeloid cells in bone marrow. A study by Siddique et al[17] andHettige et al[18] showed similar results.

In our study,average duration of hospital stay in study group was significantly less (P<0.01) as compared to control group.It is similar to a study conducted by Fenny et al.[19]

CONCLUSION

Decrease in platelet count is one of the main concerns in dengue cases. Use of CPLE in such cases significantly improves platelet count and acts as a adjuvant therapy in preventing the thrombocytopenia associated complications. Further studies are needed to assess the role of carica papaya leaf products in severe forms of dengue fever cases.

LIST OF ABREVIATIONS

ALOX →12-Arachidonate 12-lipoxygenase
CPLE→Carica Papaya Leaf Extract
DENV →Dengue Virus
DHF → Dengue Haemorrhagic Fever
DSS → Dengue Shock Syndrome
ECG →Electro Cardio Graphy
ELISA→ Enzyme Linked Immuno-Sorbent Assay
Hb→Haemoglobin
HCT → Haematocrit
Ig→ Immunoglobulin
LFT → Liver Function Tests
PTAFR→Platelet Activating Factor Receptor
PCV → Packed Cell Volume
RBC → Red Blood Cell
RNA →Riboxy Nucleic Acid
RFT → Renal Function Tests
TC → Total Count
USG → Ultra SonoGraphy
W.H.O → World Health Organization
WBC→ White Blood Cell

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