

EFFICACY OF CARICA PAPAYA LEAF EXTRACT IN TREATING THROMBOCYTOPENIA IN CASES OF DENGUE

Gupta Abhishek¹, Tyagi Vinod², Malik S. K. K.³, Virmani S.K.⁴, Singhal Saurabh⁵

¹⁻⁵Department of Medicine, Subharti Medical College, Swami Vivekanand Subharti University, Meerut

Submitted on :- 18-11-2015

Resubmitted on :- 14-12-2015

Accepted on:- 15-03-2016

ABSTRACT

AIM: The study was conducted to evaluate the efficacy of Carica papaya leaf extract (CPL) to increase platelets in patients with dengue fever (DF) with thrombocytopenia. **METHOD:** The study was conducted in Chhatrapati Shivaji Subharti Hospital, Meerut. A total of 50 subjects were enrolled who had thrombocytopenia with dengue. The subjects were divided into two groups as cases and control group. The intervention group also received CPL tablets three times daily for five days. Both the groups were managed as per WHO guidelines for management of dengue. Platelet monitoring was done daily. The results showed that CPL had significantly increased the platelet count during the therapy period, in dengue fever patients, compared to the control group. Thus this study concluded that Caricapapaya leaf extract (CPL) significantly increase the platelet count in patients with dengue with thrombocytopenia.

Key Words : Dengue fever, Carica papaya, Thrombocytopenia.

INTRODUCTION

Dengue:

Dengue is probably the most important arthropod-borne viral disease worldwide. Dengue viruses (DV) belong to family Flaviviridae and have four serotypes. It is transmitted mainly by *Aedes aegypti* mosquito and also by *Aedes Albopictus*.¹ An estimated 50 million dengue infections occur annually and approximately 2.5 billion people live in dengue endemic countries.²

The 2009 WHO criteria classify dengue according to levels of severity: dengue without warning signs; dengue with warning signs; and severe dengue.

CRITERIA FOR SEVERE DENGUE:2

Severe plasma leakage leading to:

Shock(DSS)

Fluidaccumulationwithrespiratory distress

Severe bleeding as evaluated by clinician

Severe organ involvement

Liver:ASTorALT>= 1000

CNS:Impairedconsciousness

Corresponding Author:

DR. ABHISHEK GUPTA

Department of Medicine

Subharti Medical College

Meerut-250002, U.P. (India)

E-mail : vasugupta792000@yahoo.com

Heartandotherorgans

Dengue and Thrombocytopenia:

Dengue virus 2 (DV-2) is considered to be the most common virus responsible in causing infection. In an in vitro study DV-2 has shown that it inhibits megakaryopoiesis and induces cell death in precursors of megakaryocytes which leads to thrombocytopenia in dengue disease.³ One in vivo study has studied the electron microscopic interaction of dengue virus with platelets. It showed that virus directly activate the platelets and significant structural changes leading to formation of autophagosomes which leads to destruction of platelets. Another study showed endothelial cell dysfunction.⁴ There is molecular mimicry between platelets/endothelial cells and dengue virus antigens. Platelets and endothelial cells are bound by the cross-reactive anti-dengue virus antibodies such as anti-NS1 or anti-prM antibodies.⁵ This cross reactivity leads to increased peripheral platelet destruction by the dengue virus. This could be due to an autoimmune reaction, where antibodies produced by the host against the virus bring about activation and destruction of platelets.⁶ Platelets may also show an increased reaction with leucocytes and endothelial cells, leading to their destruction.^{7,8} There is Platelet dysfunction also which may be due to abnormal activation and inhibition of platelets. It may also be responsible for thrombocytopenia.^{9,10}

Treatment of dengue fever is mainly supportive. Identification of warning signs is paramount for management of dengue. Thrombocytopenia and associated bleeding manifestation is a major complication. So far there is no specific drug for the treatment of dengue. However recently alternative therapy like carica papaya leaf extract has shown to be beneficial in many in

vivo studies. So we undertook this study to test the efficacy of commercially available tablets of CPLE in treatment of dengue with thrombocytopenia.

MATERIALS AND METHODS

A randomized, case control study was conducted at Chhatrapati Shivaji Subharti Hospital, Meerut. The CPLE was used in dosage form of tablet in the strength of 1100mg. A total of 50 subjects (n=60) diagnosed as dengue cases by NS1 antigen test were enrolled and in this study after they satisfied the inclusion criteria. Of the total subjects 25 were assigned to case group where in addition to the supportive management of dengue, the investigational drug Caricapapaya leaf extract 1100mg tid for 5 days was administered.

The remaining 25 in control group received the supportive management of dengue. All the subjects were followed up every day for five days and their platelet counts were monitored daily.

INCLUSION CRITERIA

1. Age between 18 and 60 years
2. Diagnosis confirmed as DF or DHF Grade 1, Grade 2
3. Platelet count below 100,000 and above 30,000 per μL
4. ALT/SGPT level less than 165 U/L

EXCLUSION CRITERIA

1. Patient diagnosed with severe dengue
2. Platelet levels are less than 30,000 per μL
3. Has received blood products or blood transfusion
4. Patient diagnosed with ITP, Leukaemia or Hemophilia
5. Serum Creatinine more than 1.4 mg/dl (if female) or 1.5mg/dl (if male)

DIAGNOSIS OF DF OR DHF

A clinical diagnosis of DF and DHF was made by the clinician based upon the patient's presentation and blood investigations. A rapid dengue test (NS1 Ag) was used to confirm the dengue case.

TREATMENT OF THE SUBJECTS

Once, current dengue infection was confirmed, a baseline investigation of platelet count was done. Patients in the intervention group received 1100 mg t.i.d of Carica Papaya leaf extract tablet for 5 days, in addition to receiving the standard management of Dengue. The controls received the standard management only. The platelets of both the groups were monitored daily.

RESULTS

All the 60 subjects enrolled completed the study. These subjects were diagnosed as dengue cases by NS1 antigen test. After

administering the tablet Carica papaya leaf extract to the study group (n=30) every day platelets of both the groups were monitored.

DEMOGRAPHIC CHARACTERISTIC

Distribution of sex of the subjects in the two groups did not show any difference, men were more than women (Table-1).

- Above data reveals that at baseline, mean Platelet Count was 54.82 among test group, which was comparable with 51.92 among control group and the difference was not statistically significant.
- After the treatment at the end of Day 5, mean Platelet Count showed a significant increase in Test group and an insignificant rise in Control group from baseline. If compared change was more in Test group than Control group and the difference was statistically significant.

DISCUSSION

There is no specific anti viral treatment available at this point of time. Other options need to be explored to tackle dengue. Therefore in the current lieu, considerations for alternate therapies to treat the low platelet count, should be given.^{11,12} The evolution of Carica Papaya Leaf Extract in the management of thrombocytopenia associated with dengue is significant as the literature search has found several human and animal studies been conducted where extract of carica papaya leaf was used for treating thrombocytopenia associated with dengue. The results of these studies have been encouraging with platelets showing significant rising trend.¹³ It has been found that the subjects in the intervention group that received CPLE can reach faster and higher increase in platelet count compared to the control group. There were few adverse events reported related to GI disturbances like nausea, vomiting which were similar in both the groups and not related to drugs displaying the tolerability and safety of CPLE.

The finding of this study corroborates the claim that the Carica Papaya leaf extract tablet consumption during the course of dengue infection has the potential to induce the rapid production of platelets. This was clearly seen by the significant increase in the mean platelet count in the intervention group. As on date, a study in Malaysia and a pilot study in Bengaluru, India were found to have a systematic approach in evaluating the effect of the leaf extract.^{13,14} Although capsules of the extract are currently marketed in India the mode of preparation, pharmacokinetic properties and the absorption of the active ingredient are still grey areas to be addressed.¹⁴ Hopefully in future, this can be meted out by conducting large-scale studies in DF confirmed human subjects.

CONCLUSION

Papaya extract no doubt offers a cheap and possibly effective

Table-1 : Gender comparisons of Dengue patients (n=60)

| Variables | Subjects (%) n=60 |
|-----------|-------------------|
| Sex | |
| Male | 44 (73.34) |
| Female | 16 (26.66) |

Table-2 : Age Distribution

| Age Groups (Years) | Test | | Control | |
|--------------------|------|------|---------|------|
| | No. | % | No. | % |
| 18 - 25 | 04 | 13.3 | 04 | 13.3 |
| 26 - 35 | 15 | 50.0 | 15 | 50.0 |
| 26 - 45 | 07 | 23.4 | 07 | 23.4 |
| 46 - 55 | 04 | 13.3 | 04 | 13.3 |
| Total | 30 | 100 | 30 | 100 |

By Chi- Square Test

p> 0.05, Not Significant

Table-3 : Comparison of changes in mean platelet count between the groups

| Duration | Mean Platelet Count (X ± SD) | | |
|---------------------------------|------------------------------|------------------------|----------------------|
| | Test (N = 30) | Control (N = 30) | Comparison (p value) |
| Day 1 | 54.82±20.88 | 51.92±17.80 | 0.956 (NS) |
| Day 2 | 53.86±18.19 | 58.19±16.19 | |
| Day 3 | 65.14±16.27 | 56.69±19.02 | |
| Day 4 | 82.69±20.12 | 55.69±19.86 | |
| Day 5 | 110.71±30.57 | 75.63±22.49 | |
| Difference (Day 1- 5) (p value) | *39.89±38.50 (0.002) | 00.71±24.76 (0.913) NS | *0.003 |

By Student t Test

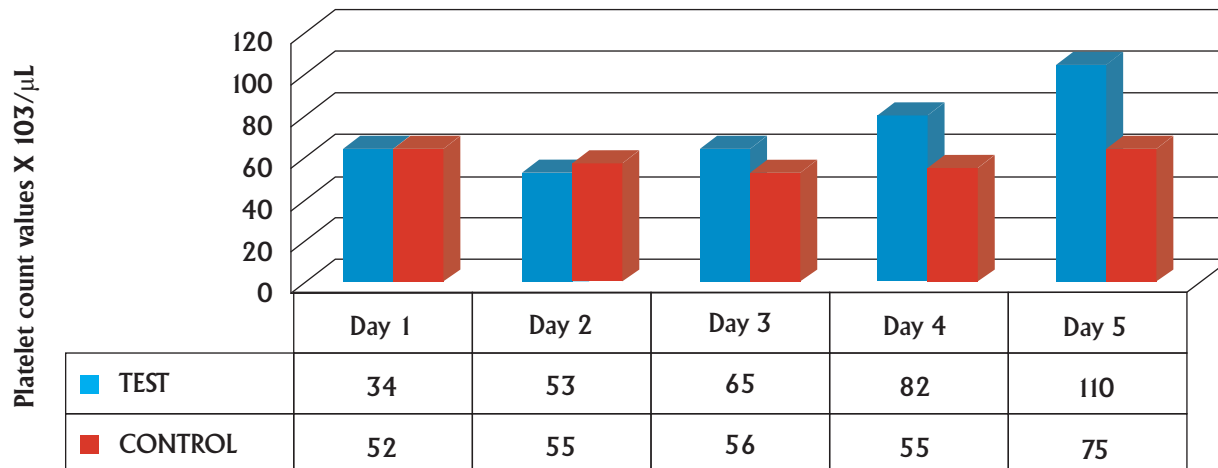
*Significant

NS= Not Significant

treatment for dengue. The current study also demonstrates the same positive beneficial trend in increasing the platelets significantly. However, large scale randomized clinical trials are

necessary to further establish its pivotal role in the management of dengue.

Graph-1 : Mean platelet count in test and control group



REFERENCES

- Gupta Nivedita ; Srivastava, Sakshi Jain, Amita Chaturvedi, Umesh C. Dengue in India; Indian J Med Res. 2012;373-390.
- WHO. Dengue: Guidelines for diagnosis, treatment, prevention, and control in sub-Saharan Africa and 13 countries in South America. Geneva: World Health Organization; 2009, 2012.
- Basu A., Jain P., Gangodkar S., Shetty S., Ghosh K.– Dengue 2 virus inhibits in vitro megakaryocytic colony formation and induce apoptosis in thrombopoietin-inducible megakaryocytic differentiation from cord blood CD34+ cells. FEMS Immunol Med Microbiol 2008;53: 46-51.
- Ghosh K., Gangodkar S., Jain P., Shetty S., Rajee S., Poddar P., et al. – Imaging the interaction between dengue 2 virus and human blood platelets using atomic force and electron microscopy J Electron Microsc 2008; 57 : 113-118.
- Huan-Yao Lei, Kao-Jean Huang, Yee-Shin Lin, Trai-Ming Yeh, Hsiao-Sheng Liu and Ching-Chuan Liu. – Immunopathogenesis of Dengue Hemorrhagic Fever; American Journal of Infectious Diseases 2008; 4 (1): 1-9.
- Lin C.F., Wan S.W., Cheng H.J., Lei H.Y., Lin Y.S.– Autoimmune pathogenesis in dengue virus infection. Viral Immunol 2006; 19:127-132.
- Krishnamurti C., Peat R.A., Cutting M.A., Rothwell S.W. – Platelet adhesion to dengue-2 virus-infected endothelial cells. Am J Trop Med Hyg 2002; 66:435-441.
- Tsai J.J., Jen Y.H., Chang J.S., Hsiao H.M., Noisakran S., Perng G.C. – Frequency alterations in key innate immune cell components in the peripheral blood of dengue patients detected by FACS analysis. J Innate Immun 2011; 3:530-540.
- Ghosh K., Gangodkar S., Jain P., Shetty S., Rajee S., Poddar P., Basu A. – Imaging the interaction between dengue 2 virus and human blood platelets using atomic force and electron microscopy. J Electron Microsc 2008; 57: 113-118.
- Noisakran S., Choekphaibulkit K., Songprakhon P., Onlamoon N., Hsiao H.M., Villinger F., Ansari A., Perng G.C. – A re-evaluation of the mechanisms leading to dengue hemorrhagic fever. Ann NY Acad Sci 2009; 1171:E24-E35.
- Adopted from Sudhir S. Sekhon, Vivek Roy, – Thrombocytopenia in Adults: A Practical Approach to Evaluation and Management. Southern medical journal 2006;99(5):491-98.
- Arnold DM, Kelton JG. Current options for the treatment of idiopathic thrombocytopenic purpura. In Seminars in hematology 2007 Oct 31 (Vol. 44, pp. S12-S23). WB Saunders.
- Gowda AC, Vijay Kumar NB, Kasture PN, Nagabhushan KH. A pilot study to evaluate the effectiveness of Carica papaya Leaf extract in increasing the platelet count in cases of dengue with thrombocytopenia. Indian Med Gaz 2015; 149:109-16.
- Ansari RM. Extract of Carica papaya L. leaves: Standardising its use in dengue fever. Indian J Pharmacol 2016;48:338-9.

