



THE EFFECTIVENESS OF CARICA PAPAYA LEAF EXTRACT IN CHILDREN WITH DENGUE FEVER

Dr. Deepa Shetty*, Dr. Anita Manoj, Dr. Dipti Jain, Dr. Mangala Narayane and Dr. Amit Rudrakar

Department of Paediatrics, Dr Babasaheb Ambedkar Memorial Central Railway Hospital Byculla.

*Corresponding Author: Dr. Deepa Shetty

Department of Paediatrics, Dr Babasaheb Ambedkar Memorial Central Railway Hospital Byculla.

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ABSTRACT

Introduction: Thrombocytopenia is almost always seen in dengue fever. Carica papaya leaves have been used before considering their beneficial effect on platelets. There are very few studies available testing their effects in children with dengue. **Aim:** To study the effectiveness of carica papaya leaf extract in children with dengue. **Materials and Methods:** A single centre, comparative study was conducted. Children aged 1 to 16 years with dengue and platelets $\leq 1.5 \times 10^5$ per μL and $\geq 50 \times 10^3$ per μL were included. Thirty children were assigned to either test or control group. Carica papaya leaf extract formulated in appropriate dosage form of tablet in the strength of 1100mg for children above 12 years, syrup as (275mg/5ml) 10ml for children between 6 to 12 years and 5 ml for children below 6 yrs was given thrice daily for 5 days to test group in addition to the routine symptomatic treatment given to the control group. The platelets were monitored and compared across the two groups. **Results:** Thirty patients were included and in those 21 were male. Mean baseline platelet of test and control group were comparable 1,43,270 per μL and 1,48,200 per μL respectively ($p=0.76$). There was no significant difference in mean platelet count at the end of treatment on day5, 1,62,933 per μL v/s 1,97,333 per μL in test v/s control group ($p=0.15$). **Conclusion:** Carica papaya leaf extract, showed an increasing trend in the platelets in dengue comparable to the control group and it coincided with the natural increase in platelets in the recovery phase. Carica papaya leaf extract has no side effect in children with dengue.

KEYWORDS: Carica papaya, dengue, thrombocytopenia.

INTRODUCTION

Dengue is the most common arthropod-borne viral illness in humans. The incidence has increased 30-fold in the last five decades. Dengue is transmitted by mosquitoes of the genus *Aedes* species *aegypti*.^[1] About 2.5 billion population i.e approximately 40% of world population live in the 100 endemic countries and areas where dengue viruses can be transmitted. Upto 50 million infections occur annually with 5,00,000 cases of dengue haemorrhagic fever and 22,000 deaths mainly among children.^[2] According to the data of National Vector Borne Disease Control Programme (NVBDCP), the number of cases reported in India in 2017 was 1,88,401 for dengue with 325 deaths.^[3] The Dengue viruses (DV) belong to family flaviviridae and there are four serotypes of the virus.

The main mechanisms causing dengue induced thrombocytopenia include impaired thrombopoiesis and peripheral platelet destruction.^[4] Altered proliferative capacity, inhibition of differentiation and megakaryocytic progenitor apoptosis are other possible mechanisms of thrombocytopenia. Dengue fever in children is characterised by continuous fever lasting for

or upto a week, haemorrhagic or bleeding tendency, thrombocytopenia, evidence of plasma leakage, low platelet count and third space effusion.^[5]

Young children and infants in particular may be less able to compensate for capillary leakage and are consequently at greater risk of dengue shock.^[5] The management of dengue fever is essentially symptomatic as no specific treatment is available.^{[6],[7]} No licensed dengue vaccine is available and several vaccine candidates are currently being evaluated in clinical studies.^[4] Therefore there is an increasing need of development of an alternative therapy for dengue. It has been reported previously that several plant species prevent complication of thrombocytopenia but do not cure dengue. Ayurvedic literature reveals that papaya leaf extract has haemostatic and other medicinal properties.^[8-11] Further mass media revealed the beneficial effects of papaya leaf extract in Asian patients who have dengue haemorrhagic fever.^[12] No formal research has been done on the subject in children. However, there are studies conducted on adults.^{[4],[13]} The evolution of Carica Papaya leaf extract (CPL) in the management of thrombocytopenia associated with dengue is significant as it would be a

better option in fever associated with thrombocytopenia, palatable, with no side effects, reducing the cost of hospitalisation, accessible and decreasing the mortalities. The study was conducted to evaluate whether Papaya leaf extract can be used to treat low platelet count associated with dengue in children.

MATERIALS AND METHODS

A single centre comparative study was conducted after institutional ethical committee clearance (Registration no: EC/BYC/11.10.2017/Dr.D.R.S). The study was conducted over a period of three months from October 2017 to December 2017. Carica papaya leaf extract formulated in appropriate dosage form of tablet in strength of 1100mg and syrup as (275mg/5ml) was procured. The variable used for sample size calculation was platelet count, power of study was 80% and CI was 95%. Children upto 16yrs were included after written informed consent from their parents. Diagnosis of dengue fever was confirmed by the Ns1Ag test. Children with platelet count $\leq 1,50,000$ per μ L and $\geq 50,000$ per μ L were included. Their ALT/SGPT levels were less than three times normal for age i.e 5-35U/L. Children diagnosed with severe dengue or dengue shock syndrome, platelets below 50,000per μ L who had received blood products during or within 3months of diagnosis or children with bleeding disorders or alternative diagnosis (malaria) were excluded from the study. Blood samples were collected in EDTA anticoagulated vials and platelet counts were measured by automated count analyzer. Platelet counts were obtained at baseline and on a daily basis for next four days. Platelet increment for the last day was calculated using following formula: Platelet increment on Day 5 = Platelet count on day 5 - Baseline platelet count. Thirty

children (n=30) diagnosed as dengue cases by Ns1Ag test were enrolled and randomized in this study. Fifteen out of thirty children were randomized to test group where in addition to the supportive management of dengue Carica papaya leaf extract 1100mg as tablet was given three times a day for children above 12 years, 550mg as syrup three times a day for children between 6 to 12years and 250mg three times a day for children below 6 years for 5 days were administered. The dosage was decided as per the recommendation of the drug company manufacturing the carica papaya leaf extract formulation. The remaining fifteen children in control group received the routine supportive treatment of dengue. All the subjects were followed up daily for five days from starting Platfast and their platelet count was monitored daily. Patients were inquired about any side effect during the study period. The platelet increment on Day 5 as compared to the nadir of platelet count on Day 3 was calculated using formula: Platelet count on Day 5 – Platelet count on day 3 of study.

STATISTICAL ANALYSIS

Data was analyzed using SPSS Statistics software Version 16. Patient characteristics were compared with the use of the chi-square or Fisher's exact test for categorical variables. Independent sample T test was used for continuous variables (platelet increments at the end of 5 days). A one-sided $p < 0.05$ was considered to be statistically significant with the confidence interval of 95%.

RESULTS AND DISCUSSION

There were 30 children included in which boys were more than girls. Most children infected are in the age of 9-12 years old followed by 5-8 years old (table1).

Age Groups (Years)	Test	Control
	No.(%)	No.(%)
1-4	02(13.3)	01(6.7)
5-8	03(20.0)	05(33.4)
9-12	09(59.9)	07(46.7)
13-16	01(6.7)	02(13.4)
Total	15(100)	15(100)
By Chi—Square Test $p > 0.05$, Not Significant		

Table 2 Reveals that, 73.3% of cases among test group were male which was comparable to 66.7% of male

cases among control group and the difference was not significant.

Gender	Test	Control
	No.(%)	No.(%)
Male	11(73.3)	10(66.7)
Female	04(26.7)	05(33.3)
By Chi-Square Test $p > 0.05$, Not Significant		

The platelet counts of children in the test group was lower than the platelet counts in the control group and they reached a nadir after which they showed an

increasing trend coinciding with the natural course of platelets in dengue and the monitoring of platelets clearly

indicated that the change in the platelet count is faster in the test group as compared to the control group (**table 3**).

Duration	Mean Platelet Count (X±SD)x 10 ³ per µL		
	Test(N=15)	Control(N=15)	Comparison (p value)
Day 1	143.27±37.94	148.20±48.95	0.760(NS)
Day 2	107.33±44.03	137.67±53.45	
Day 3	86.13±47.58	121.67±50.55	
Day 4	97.47±48.10	148.67±43.51	
Day 5	162.93±69.48	197.33±57.96	0.152
Difference (Day 1-5)(p value)	19.67±85.32 0.387(NS)	49.13±51.27 0.002*	0.261(NS)
By Student t Test	*Significant NS=Not Significant		

A steep rising trend in the platelets of the test group was observed, whereas in the control group there was a gradual rise(shallow) on 4th and 5th day. The difference between the trend of platelets in test and control group however was not statistically significant. The platelets in the test group children were lower, attained a nadir and then increased faster on day3 of platfast as compared to the control group which showed an increasing trend which was gradual. This phenomenon coincided with the natural increasing trend of platelets observed in the recovery phase of the illness. **Table 3** reveals that at baseline, mean platelet count was 143.27x10³perµL among test group, which was comparable with 148.20 x10³perµL among control group and the difference was not statistically significant. In the test group the mean platelet count had fallen upto 86.13 x10³perµL before it started increasing and the increment on day 5 of the study compared to the nadir on day 3 was statistically significant(p<0.05). After the end of Day 5, mean platelet count showed an increase in the test group which was however not statistically significant. There were no side effects reported related to platfast like nausea or vomiting confirming its tolerability and safety in children.

From the literature published previously it has been proved that CPLE has beneficial properties in DF. CPLE has brought about a significant and rapid increase in platelet count. Hettige S. in 2002 had reported in the bmj regarding papaya leaves for speedy rise of platelet count in Dengue. Sathasivam et al. in 2009 reported that CPLE can increase platelet count in mice. Ahmed et al in 2011 concluded that Carica papaya leaves aqueous extract exhibited potential activity against dengue fever. Our trial is a first of its kind to be done in children unlike all the above mentioned studies. There were no side effects reported related to platfast like nausea or vomiting confirming its tolerability and safety in children. Carica papaya leaf extract, in our trial, showed an increasing trend in the platelet count in dengue fever however not statistically significant and it also coincided with the natural increase in platelet count in the recovery phase of the illness. Our trial results are comparable to the

PLEAD trial conducted by M.Z.K. Assir et al in 2012 who concluded that papaya leaf extract did not show any effect on platelet count in dengue fever.^[13] In our trial the children in the test group who received CPLE achieved faster increase in platelet count compared to the control group after the day 3 nadir however the increasing trend of platelets were comparable in both the groups as against the reports published previously, latest being that by A.C. Gowda et al in 2015 who concluded that CPLE does significantly increase the platelet count in adults with thrombocytopenia associated with dengue fever.^[4] Significant results were not obtained in children in our study as observed in previous studies in adults. All the children included in our study presented from day 1 to day 6 of onset of fever and the uniformity of the day of presentation could not be maintained. Also the details in clinical history of whether it was the first presentation of DF or relapse were not reliable. Some children got the drug during the febrile phase, some during the critical phase and most during the recovery phase of the illness. Children with platelet count below 50,000/uL were excluded from the study. Further studies are required to be done in children to obtain significant results as observed in previous studies.

CONCLUSION

Carica papaya leaf extract, showed an increasing trend in the platelet count in dengue fever comparable to the control group and it coincided with the natural increase in platelet count in the recovery phase of the illness. Carica papaya leaf extract has no side effect in children with dengue fever and low platelet count.

LIMITATIONS AND FUTURE RECOMMENDATIONS

To assess the effectiveness of Carica papaya leaf extract on platelets in children with Dengue, other parameters like day since onset of fever and starting platfast and first or repeat dengue viral infection were not monitored, also children with platelet count below 50,000/uL were not included in the study. Placebo was not added to the control group considering the more restricted use of placebo in children than in adults.

CONFLICT OF INTERESTS: No conflict of interests.

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