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Original Research Article

Therapeutic benefits of carica papaya leaf extracts in dengue fever patients

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Abstract: Carica Papaya (C. papaya) is commonly called as paw-paw and it belongs to the family Caricaceae. It have been successfully employed as a folk medicine for many years for the treatment of dengue infections with haemorrhagic manifestations. Since last few decades papaya is known for its food and nutritional values throughout the world. Currently, leaves of C. papaya possess medicinal properties and are widely used in traditional medicines. This review focuses on different properties of papaya as a multi-faceted plant. This study was conducted to evaluate the therapeutic benefits of C. papaya leaves juice on platelet and hematocrit values in patients with dengue fever. A total of 80 patients were enrolled from the tertiary healthcare center in central India. Subjects were randomized into two groups, 40 patients were intervention groups who received two C. papaya leaves extract capsules (CPC) thrice daily and rest 40 were controls. The results this study showed that administration of papaya leaf juice was beneficial in dengue patients in elevating the platelet count ($p<0.05$) and maintained stability of hematocrit in the normal level in those patients who were subjected to C. papaya leaves extract capsules. In conclusion the Carica papaya leaf extract could be used as an additional or as a complementary drug in dengue fever patients with thrombocytopenia; it accelerates the increase in the platelet count and shorten the hospitalization thereby reducing the cost of hospitalization significantly.
Keywords: Carica, Dengue fever, Hematocrit, Thrombocytopenia

INTRODUCTION

Dengue is the most common mosquito borne arboviral disease affecting human beings and is a leading cause of morbidity and mortality in the tropics and subtropics regions. It belongs to Flaviviridae family and is transmitted by the mosquitoes Aedes aegypti [1]. It produces a wide spectrum of clinical illness, ranging from an asymptomatic or mild febrile illness, classic dengue fever to the most severe form of illness; dengue haemorrhagic fever (DHF), which results from severe thrombocytopenia [2].

Carica papaya (C. papaya) is a member of the caricaceae and is a dicotyledonous, polygamous and diploid species [3]. It originated from Southern Mexico, Central America and the northern part of South America. It is now cultivated in many tropical countries such as India, Bangladesh, Indonesia, Sri Lanka, Philippines, West Indies and Malaysia. The papaya fruit is globally consumed either in its fresh from or the form of juices jams and crystallized dry fruit. The ripe fruit is said to be a source of vitamin A, C and calcium. There are many commercial products derived from the different parts of the C. papaya plant, the most prominent being papain and chymopapain which is produced from the latex of the young fruit, stem, and the leaves. C. papaya leaves have been used in folk medicine for centuries. Recent studies have shown its beneficial effect as an anti-inflammatory agent, for its wound healing properties [4] anti-tumor as well as immunomodulatory effects [5] and as an antioxidant [6]. A toxicity study (acute, subacute, and chronic toxicity) conducted on Sprague Dawley rats administered with C. papaya leaves juice revealed that it was safe for oral consumption[7]. Safety studies based on OECD (Organization of economic Cooperation and development) guidelines for acute, subacute and chronic toxicity conducted on C. papaya extract and showed that it was found to be safe for human consumption [7].

The leaves of papaya have been showed to contain many active components. That can increase total antioxidant activity in blood and reduce lipid peroxidation level, such as paper chymopapain, cystatin, tocopherol, ascorbic acid, flavonoids, and cyanogenic-glycosides glucosinolates [5].

The alkaloids, flavonoids, saponins, tannin, and glycosides are related with anti-inflammatory

activity. C. papaya leaves extract also found to have anti-bacterial effect [8], anti tumor, and immunomodulation activities. The leaf of C. papaya is categorized as non toxic because it's LD50 >15 g per kg body weight. The leaves also contain cardiac glycosides, anthraquinones, carpaine, pseudocarpaine, phenolic compounds [9, 10].

In addition to the nutritional value of its fruit, the leaves of C. papaya possess medicinal properties and are widely used in traditional medicines. Previous studies in papaya have shown that seed extract of C. papaya possess pharmacological activities, including antihelmintic, antifertility, contraceptive etc. A hot-water extract of the leaves is taken orally as an antipyretic, treatment of anemia and appetite stimulation. In other countries the leaves extract of C. papaya had been effectively used for treatment of dengue fever disease associated with thrombocytopenia [11].

MATERIALS AND METHODS

Study Design:

In this observational single center prospective study, a total of 8o cases was analyzed amongst which 40 were dengue patients who received two C. papaya leaves extract capsules (CPC) thrice daily and rest 40 were not given capsules and was categorized as controls. This study was conducted on patients getting admitted to Medicine Department of a tertiary care center, Indore from September 2014 to September 2015. Before screening all participating patients received full verbal and written details of the study including study procedure and use in the subject information sheet. Before enrolling, informed patient consent was obtained by their signing of the informed consent form.

Clinical Assessments:

At screening, enrolment was based on eligibility criteria, medical history and clinical examination. Demographic information such as age, sex, height and weight were recorded. Pre-study physical examination was carried out at physician's discretion. All information obtained during screening was entered in the case report form.

We included adult males or females with age more than 18 years; patients with fever of less than one month duration, platelet count less than 100000/µl and voluntary patient consent. All pregnant and lactating females were excluded from the study. Patients < 18 years; and with history of allergic drug reactions were excluded from the study. Clearance was gained from our institutional ethical and research committee before conducting this study.

Laboratory measurements:

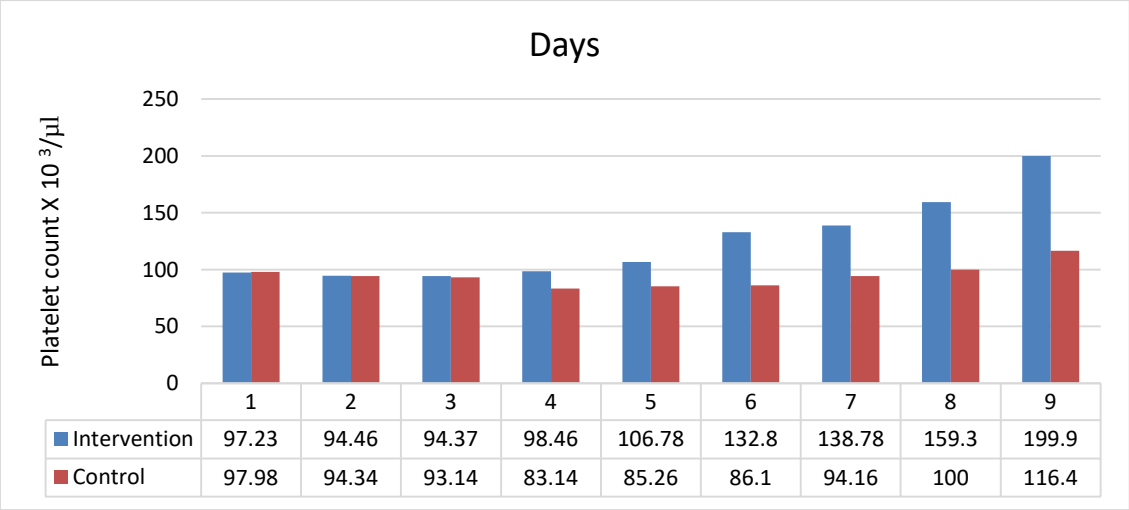
All the routine blood investigations were done as per standard protocol. Complete blood count was performed on automated Sysmex Kx-21(Transasia-Japan). All biochemical tests were performed by fully automated VITROS® dry chemistry analyzer. Erythrocyte Sedimentation Rate (ESR) is determined in EDTA tube using Wintrobe's Method.

Statistical Analysis:

Data was entered in Microsoft excel 2007 and analyzed on MedCalc Software (Trial Version). Student t test was applied to see the difference in mean in two groups. p value less than 0.05 was considered significant.

RESULTS

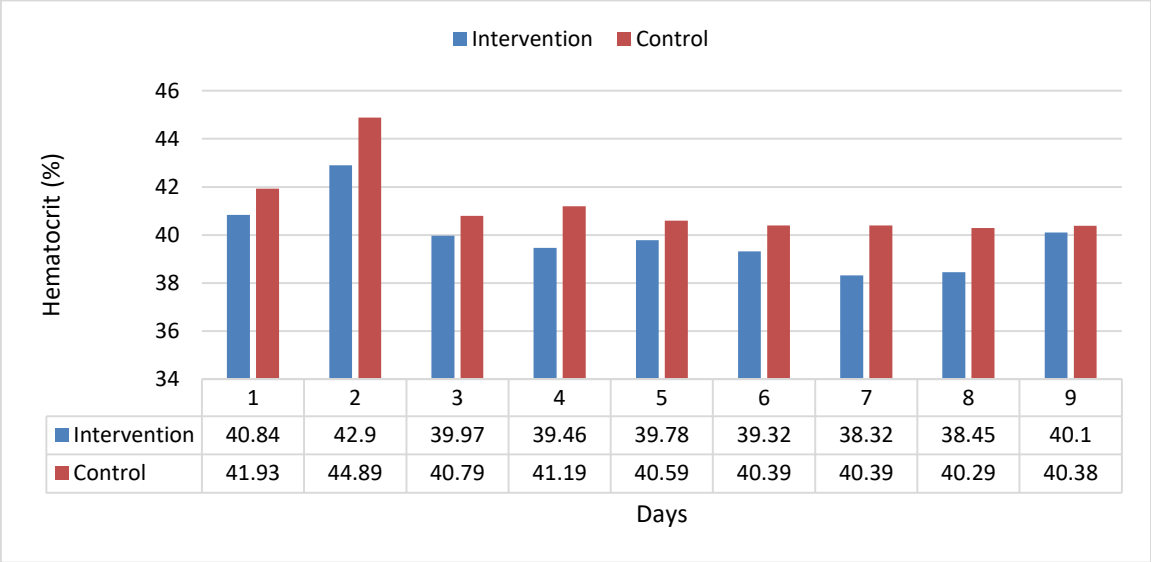
The result showed that CPC had significant increased the platelet count ($p<0.05$) and maintained stability of hematocrit in the normal level.



	1	2	3	4	5	6	7	8	9
Intervention	97.23	94.46	94.37	98.46	106.78	132.8	138.78	159.3	199.9
Control	97.98	94.34	93.14	83.14	85.26	86.1	94.16	100	116.4

Fig-1: Graph showing the change in platelet count of all subjects

The rise of platelet counts in the intervention group is 'J' shaped and shallow 'u' in the control group respectively, demonstrating faster and significant rise of platelets during the critical phase of defervescence (Figure1). Statistical analysis with dependent t test showed significant differences of platelet count ($p<0.05$).



	1	2	3	4	5	6	7	8	9
Intervention	40.84	42.9	39.97	39.46	39.78	39.32	38.32	38.45	40.1
Control	41.93	44.89	40.79	41.19	40.59	40.39	40.39	40.29	40.38

Fig-2: Graph showing the change in hematocrit levels (%) of all subjects

Hematocrit levels remained stable in intervention group but change in hematocrit levels in intervention and control group were statistically insignificant (Figure 2).

DISCUSSION

Thrbocytopenia often characterized by platelet count less than 150000 per µl of blood is more prevalent and could be due to a decreased platelet production and/or increased destruction. Thrombocytopenia is associated with symptoms as bruising, purpura in forearms, pinpoint hemorrhages, nose bleeds, and bleeding gums. Clinical manifestations of Thrombocytopenia are mild as long as platelet counts are above 20,000/µl and are generally limited to easy bruising. Once the count goes below 10000/µl the risk of spontaneous mucocutaneous bleeding (gingival bleed, epistaxis, menorrhagia, petechiae and ecchymoses) and life threatening spontaneous intracranial hemorrhage or gastrointestinal bleeding increases rapidly [12].

Treatment is guided by etiology and disease severity. The main concept in treating thrombocytopenia is to eliminate the underlying problem, whether that means discontinuing suspected drugs that cause thrombocytopenia, or treating underlying sepsis. Corticosteroids, intravenous immunoglobulin, and splenectomy remain mainstays of treatment however, newer therapies including rituximab and the thrombopoietin receptor agonists are remodeling conventional treatment algorithms. In severe cases and associated with bleeding platelet transfusion is recommended.

All these above mentioned treatment options have their own advantages and disadvantages. Therefore in the current lieu, consideration for alternate therapies to combat the low platelet count, which is relatively free from the toxic side effects of the drug, should be given.

Certain genes have been shown to influence platelet production and platelet aggregation, namely the Arachidonate 12-lipoxygenase (ALOX 12) also known as the Platelet-type Lipoxygenase as well as the Platelet-Activating Factor Receptor (PTAFR). An increase in activity of these genes is required for platelet production and activation. The ALOX 12 gene is strongly expressed in megakaryocytes and has been known to be responsible for the 12-Hydroxyeicisatetraenoic acid (12-HETE) production of platelets [13]. The PTAFR gene has been found to be expressed in megakaryocytes indicating that it could be a precursor for platelet production in addition to its well known role in platelet aggregation. ALOX 12 is known to be associated with increased megakaryocyte production as well as its conversion to platelets through 12-HETE mediated pathway which in turn leads to increased platelet production. The active ingredients of C. papaya up regulate the ALOX 12 and PTAFR gene thereby leading to an increased production of megakaryocytes and its conversion into platelets. Clinical evidence shows that. C. papaya extract increases ALOX 12 activity 15 fold and PTFAR

activity 13.42 fold which is responsible for increased platelet production [14].

Fenny Yunita *et al.;* showed that C. papaya leaves juice significantly accelerates the rate of increase in platelet count among patients with dengue fever and dengue hemorrhagic fever[15]. Nisar Ahmed demonstrated rise of platelet count from 55000/µl to 168000/µl after C. papaya leaves extract in dengue fever patient[16]. Our study results were also consistent with these previous studies.

CONCLUSION

C. papaya leaf extract could be used as an additional or as a complementary drug in acute febrile illness patients with thrombocytopenia; it accelerates the increase in the platelet count and shorten the hospitalization thereby reducing the cost of hospitalization significantly.

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