

## EDITORIAL

# Role of Carica papaya Leaf Extract for Dengue Associated Thrombocytopenia

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Dengue is one of the most important arthropod-borne disease worldwide, due to the sheer number of cases per year (estimated 50-100 million) and the fact that billions of people are vulnerable to dengue due to international travel and spreading of mosquitoes from tropical countries to non-tropical areas. World Health Organization estimates that almost half the world's population lives in countries where dengue is endemic.<sup>1</sup> Dengue is caused by dengue virus (DENV) 1-4 through *A. aegypti* mosquitoes as the predominant vector. The disease presents with sudden onset fever, frontal headache, generalized myalgia, retro-bulbar pain and transient macular skin rash after an incubation period of 4-7 days of infected mosquito bite. The body pain is sometimes so severe that it is synonymously called "break-bone fever." The diagnosis of dengue infection is made clinically on the basis of fever, myalgia and skin rash during an epidemic and confirmed by laboratory investigation. Thrombocytopenia is the hallmark finding in dengue patients, which usually develops after the initial acute "febrile phase" of dengue, which last for 3-5 days. This is followed by "critical period" 24-48 hours duration and lastly by "recovery phase." The laboratory confirmation is done by NS1 antigen detection by ELISA and RT-PCR during initial 4-5 days. Positive IgM ELISA and rising paired serology during recovery phase are usually done after 5 days of dengue infection for

confirmation, as antibody response is negative in early stage of dengue.

Most of the patients do not develop 'severe' dengue, which needs close monitoring and hospital admission for management of bleeding, hypotension and other complications. 'Severe dengue' term is used for the cases with significant bleeding, patient with compensated or profound shock (dengue hemorrhagic fever III/IV) or patients with expanded dengue syndrome<sup>2</sup> (severe hepatic, renal dysfunction etc.). It is estimated that annually approximately 500,000 cases of severe dengue occur worldwide with case fatality to the tune of around 2.5%, which can be improved to <1% with good management. There are no effective antiviral agents against dengue virus therefore the treatment remains supportive. The most common cause of fatality is due to refractory shock due to capillary leakage secondary to increased vascular permeability or bleeding. Therefore the most important investigation for management of dengue patient is hematocrit or packed cell volume (PCV) and not platelet value. The indication of platelet transfusion is only in cases of bleeding secondary to thrombocytopenia and most of the international and national guidelines suggest platelets should not be transfused prophylactically unless platelet is markedly low (<10,000/ $\mu$ L) as platelet transfusions can be more

harmful in un-indicated cases. The crystalloid should be transfused as rapid bolus or continuous infusion depending on hematocrit value and blood pressure. Patients who do not respond with initial fluid management should be treated with repeat crystalloid infusion, colloid infusion or blood transfusion according to individual case scenario.

However, there is a lot of panic regarding the platelet counts in dengue season. Any patient of fever with thrombocytopenia causes panic amongst the patient and relative's about possibility of dengue. Thrombocytopenia is an important pointer to the diagnosis of dengue for the lay-person and the general physician. Also thrombocytopenia is a contributor to bleeding, which appear to be the root cause to the patient and relatives, and therefore correction of the same may be a priority for the patient, although correction of thrombocytopenia does not figure as one of the mainline principles of dengue management. There remains a lot of hue and cry about lack of agents, which can raise platelet counts, and shortage of platelet transfusions in the dengue season. People resort to a number of untested and unverified preparations and local remedies in order to increase their platelet counts with or without success. Papaya leaves are believed to have some role in the same, although

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**Fig. 1: *Carica papaya***

authentic published evidence had been lacking until now.

*Carica papaya* (Figure 1) is commonly known as papaya and in Hindi language it is called "Papita". The Sanskrit name is 'Chirbhita'. Papaya plant is native to Central America and it is believed that its use in India started around 17<sup>th</sup> century. It is now cultivated throughout the world. The therapeutic effects of *Carica papaya* leaves are presumed to be due to several active components such as papain, chymopapain, cystatin, L-tocopherol, ascorbic acid, flavonoids, cyanogenic glucosides and glucosinolates.<sup>3</sup> Animal studies suggest that papaya leaf extracts have potential therapeutic effect on disease processes causing destabilization of biological membranes as they inhibit hemolysis *in vitro*.<sup>4</sup> They may cause increased platelet and red blood cell counts.<sup>5</sup> A recent open-labeled trial from Malaysia demonstrated significantly higher platelet count after 40-48 hours of first dose of papaya leaves juice.<sup>6</sup> Others have also reported similar encouraging findings. In spite of these small-scale studies, the fact remains that dengue is mostly a self-limiting disease with

spontaneous increase in platelets during recovery phase.

In this issue of journal two well-designed placebo controlled randomized trials from India are being published to evaluate the efficacy of *Carica papaya* leaf extract (CPLE) in improving platelet count in patients of dengue. Both the studies had minor differences in inclusion and exclusion criterion and the strength of CPLE capsule used, but the primary aim was the same, to increase the platelet count in dengue subjects. The study by Kasture PN et al, was a multi-centric, double blind, placebo controlled, randomized, observational study conducted in 300 patients across 5 centers in India, to evaluate the efficacy and safety of CPLE, as empirical therapy for thrombocytopenia associated with dengue fever.<sup>7</sup> Both the randomized groups (interventional and control) were managed by the standard management guidelines for dengue. In addition to this, the intervention/test group received CPLE tablet (1100 mg) three times a day for five days. All of them were followed daily with platelet count monitoring. The study was also registered in the clinical trial registry-India. The results indicate that CPLE had significant increase ( $p < 0.01$ ) in the platelet count over the five-day therapy duration in dengue patients, compared to the control group. There were few adverse events related to GI disturbance like nausea and vomiting which were similar in both groups. The study included maximum number of dengue patient enrolled till date worldwide for CPLE use (ayurvedic preparation) but the cohort of patients enrolled were of non-severe dengue only as the study excluded DHF grade III/IV and patients with platelet count  $< 30,000/\mu\text{L}$ . In this interventional group of non-severe dengue the CPLE tablets showed improvement in platelet count from day 2 and by day 5 the difference between the two groups was significant.

There was no significant difference between the hematocrit of the two groups after five days. Authors also declared that there was no increase in nausea or vomiting in the test group even after 5 days treatment although it was expected to have some increase in test group considering bitter taste of papaya leaf, which may have been taken care of due to capsulated formulation of CPLE used in the trial. Twelve patients (8.3%) in control group required platelet transfusion for  $< 20,000/\mu\text{L}$ , while none required in test group.

In the second single center randomized study by Gadhwal AK et al, which included 400 patients of dengue.<sup>8</sup> The test group was given locally prepared CPLE capsule of only 500 mg at dose once daily with routine supportive treatment for consecutive five days while control group received supportive treatment only. The authors observed from 3<sup>rd</sup> day onwards platelet count of test group increased significantly compared to control group ( $82.96 \pm 16.72$ ,  $66.45 \pm 17.36$  thousands,  $p$  value  $< 0.01$ ). On 4<sup>th</sup> and 5<sup>th</sup> day also platelet count of test group was significantly higher compared to placebo group ( $p$  value  $< 0.01$ ). But, surprisingly the effect on platelet rise was observed to be transient and by 7<sup>th</sup> day of treatment both the group had similar platelet count. The average hospitalization period of test group decreased by up to 2 days and so did the average platelet transfusion requirement (0.685 units per patient in test group vs. 1.19 units per patient in control group,  $p < 0.01$ ). The common exclusion criterion were patients with Expanded dengue syndrome (EDS) with severe liver dysfunction (ALT  $> 165$  U/L), serum creatinine  $> 1.4$  mg/dL, comorbid hematological illnesses, known cases of idiopathic thrombocytopenic purpura or hematological malignancy, recipients of blood/platelet transfusions, diseases affecting

platelet count and other cases of fever with thrombocytopenia like malaria, brucellosis, leptospirosis, and enteric fever which were ruled out by specific tests.

These two randomized study of CPLE use in dengue patient can be considered to be landmark in the field of ayurvedic preparations and in the field of Complementary and Alternative Medicine (CAM). These are the first studies from India in which such a large sample size was used scientifically and an ayurvedic preparation has been tested for evidence generation, similar to allopathic drug trials. These trials may open up new avenues for CAM to prove their efficacy and generate evidence for their rational use in different diseases. Previous to this study only one large study has been conducted from Malaysia, which included two hundred plus dengue patients only and in comparison these two studies had almost twice number of enrollment. Both the study proved that CPLE capsule preparation are safe and have early effect on improving the platelet count, at least in non-severe dengue, who are not very sick. The use of CPLE can reduce platelet requirement as well as hospital stay by few days in this subset of non-severe dengue patients. The role in severe dengue that is the leading cause of fatality needs to be evaluated in future. We should also remember that in the study there was no effect on hematocrit (Hct) concentration in both groups, and also in second study by Gadhwal AK et al, the platelet increasing effect was transient up to 6<sup>th</sup> day of dengue only.

Further studies need to be conducted before CPLE can be prescribed in all dengue cases, to know what's the best method

to make papaya leaf extract so that toxic materials like insecticide, herbicide, heavy metal contaminant are minimal in the CPLE preparations, ideal dose (500 mg/1100 mg), optimum frequency of administration (OD or TID) and optimum duration of treatment, which may be more beneficial and less harmful (nausea and vomiting may be initial presentation of warning signs in many dengue cases). The role of CPLE in severe dengue, which actually is responsible for the major mortality in dengue cases, still remains unexplored.

In present time the key to curbing dengue transmission is by focusing on the vector, using combinations of chemical and biological targeting of *Aedes* mosquitoes and management of breeding sites.<sup>9</sup> The good news in the field of dengue vaccine is that a TV003 live attenuated tetravalent DENV vaccine currently in phase 2 study, in a randomized double-blind, placebo-controlled trial has shown very encouraging results. All 21 recipients of TV003, who were re-challenged with DENV after 6 months, did not develop viremia, rash, or neutropenia. In contrast, 100% of the 20 placebo recipients developed viremia, 80% developed rash, and 20% developed neutropenia.<sup>10</sup>

The future appears to be bright for the mankind regarding dengue epidemic control, considering the positive results of papaya leaf use, its easy availability and affordability and also after success of early phase TV003 vaccine against all four strains of dengue viruses. It will be interesting to study the effect of CPLE in other diseases with low platelets especially primary and secondary thrombocytopenia.

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