Original Research Article

Role of *Carica papaya* leaf extract tablets/capsules on platelet counts in cases of dengue thrombocytopenia

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ABSTRACT

Background: Thrombocytopenia is the hallmark laboratory finding in dengue fever and leads to bleeding manifestations when reduced markedly. So, this causes panic amongst the patient and relatives about the possibility of severity and leading to various complications including bleeding tendencies. Platelet transfusion is the only definitive treatment and it is indicated only in severe cases with bleeding manifestations. Prophylactic platelet transfusion is not much useful unless it's reduced below 10,000cells/cumm. *Carica papaya* leaf extract (CPLE) are believed to have some role in improving platelets and its role is unclear. Hence, this study is taken up to evaluate the role of CPLE in improving dengue thrombocytopenia.
Methods: Total 500 patients were included in the study; out of which 380 were males and 120 were females. Patients of dengue fever with thrombocytopenia (Platelet count <1, 50,000 cells/cumm) matching inclusion criteria were included in the study. After the inclusion, patients were randomized into two groups. Study group and control group by simple randomization (even/odd method). The study group treated with CPLE 1100mg three times daily for five days along with symptomatic and supportive treatment. The control group was given only symptomatic and supportive treatment. The average platelet count, average duration of stay and transfusion requirement of platelets were compared using student 't' test.
Results: Increased platelet counts were noted early in the treated group than the controlled group. The average duration of hospital stay was 5.42±0.98 days in study group and 7.2±0.97 days in controlled group. The requirement of platelets is more in control group than study group and it was statistically significant.
Conclusions: *Carica papaya* leaf extract tablets can be used in patients with dengue thrombocytopenia with clear advantages over control group.

Keywords: *Carica papaya* leaf extract, Dengue, Platelets, Thrombocytopenia, Thrombocytopenia

INTRODUCTION

Dengue is the most common arthropod borne viral illness (arbovirus). It is transmitted by mosquitoes of species aedes. In the last 50 years; incidence has increased 30-fold. An estimated 2.5 billion people accounting to 40% of world population live in over 100 endemic countries and areas where dengue viruses can be transmitted. Up to 50 million infections occur annually with 500 000 cases of dengue haemorrhagic fever and 22,000 deaths mainly among children. The emergence of dengue in India has gone into epidemic proportions and dengue outbreaks are frequently engulfing different parts of the country in both urban and rural populations.[1] Dengue infections may vary from flu-like self-limiting illness to life-threatening dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) which can be fatal, if left untreated. The mortality rates with dengue have been reported to be as

high as 20%.[2] The clinical manifestations of dengue include; high grade fever, headache, arthalgia, retro orbital pain, back pain with flu like symptoms. Most common signs are conjunctiva ingestion and peticheal haemorrhages. It can cause gum bleed, upper GI bleed, haematuria, bleeding rectum and other life-threatening bleeding manifestations if associated with severe thrombocytopenia. The hallmark laboratory findings include: thrombocytopenia, leucopenia and raised haematocrit values.

The mainstay of treatment for dengue is intravenous fluids and supportive treatment. Haematocrit is the guide for the fluid management. The role of blood transfusion is limited to severe thrombocytopenia (<10,000 cells/cumm) or bleeding manifestations. There are no proven medicines are active against dengue thrombocytopenia. The CPLE have proposed to have some role in improving symptoms of dengue as well as improving platelet counts. Hence this study was taken up to assess the role of CPLE in dengue thrombocytopenia.

METHODS

This study was conducted in tertiary care teaching Hassan institute of medical sciences, Hassan, Karnataka from June 2017 to March 2018. Total 500 patients were included in the study; out of which 380 were males and 120 were females.

Inclusion criteria

- Proven cases of dengue fever
- Age >16 years and <65 years
- Platelet count <1,50,000 cells/cumm.

Exclusion criteria

- Age <16 years
- Severe thrombocytopenia (<50,000cells/cumm)
- Other causes of thrombocytopenia like malaria, severe sepsis, drug induced thrombocytopenia and pancytopenia
- Patients with hepatic impairment
- Patients with renal impairment
- Pregnancy and lactation.

Patients of dengue fever with thrombocytopenia (Platelet count <1, 50,000 cells/cumm) matching inclusion criteria were included in the study. Diagnosis of dengue was made by positive NS1 antigen test and IgM antibodies. Patients with other causes of thrombocytopenia, aged <16 years, pregnancy, lactation, hepatic impairment, renal impairment and severe dengue were excluded from the study.

After the inclusion, patients were randomized into two groups. Study group and control group by simple randomization (even/odd method). The study group

treated with CPLE 1100mg three times daily for five days along with symptomatic and supportive treatment. The control group was given only symptomatic and supportive treatment. Complete blood count, haematocrit, liver function test, kidney function test and blood sugar levels were done on daily basis in both groups. Patients were monitored from the admission till discharge. The average platelet count, average duration of stay and transfusion requirement of platelets were compared using student 't' test.

RESULTS

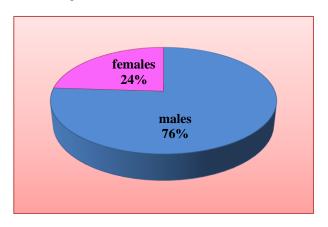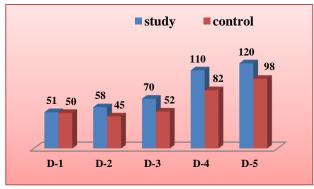Out of 500 patients, 380 were males and 120 were females (Figure 1).

Figure 1: Sex-wise distribution of the patients included in the study.

Vertical axis describing platelet counts in thousands and horizontal axis indicates days.

Figure 2: Average platelet count in the study and control population.

Most of them were in the age group of 30-40 years. Increased platelet counts were noted early in the treated group than the controlled group. Side effects like nausea, hiccoughs and loose stools noted in study group.

No significant differences in platelet count noted among both groups on first day. On second day, platelet count started increased in study group. On fifth day, platelets in study group increased faster and significantly than controlled group (Figure 2).

The average duration of hospital stay was 5.42±0.98 days in study group and 7.2±0.97 days in controlled group.

Authors followed the platelet transfusion criteria of; platelet count <20,000cells/cumm, platelet count <50,000 cells/cumm with bleeding manifestations. Total 50 patients out of 250 were transfused with platelets in study group. Total 108 patients out of 250 were transfused with platelets in control group. The requirement of platelets is more in control group than study group and it was statistically significant.

DISCUSSION

Dengue (pronounced Den' gee) is a disease caused by any one of closely related dengue viruses (DEN1, DEN 2, DEN 3 and DEN 4).[3] The Asian genotypes of DEN-2 and DEN-3 are frequently associated with severe disease. Dengue virus is a RNA virus of the family flaviviridae; they are otherwise called arboviruses. They have 3 different protein molecules that form virus partied (C, prM and E) and 7 other types of protein molecules (NSI, NS2a, NS2b, NS3, NS4a, NS4b, NS5) that are found in infected host cells and are required for replication of virus.[3] There are 4 strains of virus, ex; DEN1, DEN2, DEN3, DEN4. ALL 4 serotypes can cause full blown disease. Infection with 1 serotype is believed to produce lifelong immunity to that serotype, but he can be infected with other serotypes in future.[3]

The characteristic symptoms of dengue are: a sudden-onset fever, headache (Typically behind the eyes), muscle and joint pains, and a rash; the alternative name for dengue, "break-bone fever", comes from the associated muscle and joints pains. The course of infection is divided into three phases: febrile, critical, and recovery. The febrile phase involves high fever, frequently over 40°C (104°F) and associated with generalized pain and a headache; this usually lasts 2-7 days.

Flushed skin and some small red spots called petechiae, which are caused by broken capillaries, may occur at this point. The critical phase, if it occurs, follows the resolution of the high fever and typically lasts one to two days. During this phase there may be significant fluid accumulation in the chest and abdominal cavity due to increased capillary permeability and leakage.

This leads to depletion of fluid from the circulation and organs. During this phase, organ dysfunction and severe bleeding (Typically from the gastrointestinal tract) may occur. Shock and haemorrhage occur in less than 5% of all cases of dengue but those who have previously been infected with other serotypes of dengue virus ("Secondary infection") have an increased risk of this.

The recovery phase occurs next, with resorption of the leaked fluid into the bloodstream. This usually occurs over a period of two to three days. The improvement is often striking, but there may be severe itching and a rate.

It is during this stage that a fluid overload state may occur, which if it affects the brain may reduce the level of consciousness or cause seizures.[4] Diagnosis of DV infection is routinely done by demonstration of anti-dengue IgM antibodies or by NS-1 antigen in patient's serum depending upon day of illness using ELISA kits (prepared by National Institute of Virology, Pune) and commercial kits.[5]

Molecular methods (reverse transcriptase PCR) are being increasingly used in diagnosis of DV infection. A single tube nested PCR for detection and serotyping of DV was developed and used for detection of co-infection by two viruses.[6] Thrombocytopenia is one of the associated conditions in dengue.

In this study authors observed a significant increase in the platelets in the intervention group which reaffirmed the results of earlier pilot study. It is demonstrable that the subjects in the study group that received CPLE can reach faster and higher increase in platelet count as compared to the control group. Additionally, there was significant increase in the WBC counts in the study group as compared to the control group from the baseline values. The results are corroborative to those reported by Subenthiran et al that CPLE can increase platelet count in mice, and also in dengue fever patient as reported by Gowda et al, and Subenthiran.[7,8]

CPLE is shown to increase the expression of Arachidonate 12-lipoxygenase (ALOX12) and Platelet-Activating Factor Receptor (PTAFR) gene responsible for platelet production.[8] The WBC values in both the groups showed an increasing trend after third day onwards and can be correlated to the declining viraemia at this point of time.

The increase in the WBC in the study group was significant as compared to the control group indicative of CPLE may have stimulating action at the myeloid stem cells in the bone marrow. Nwangwa et al in their preclinical study documented an increase in the WBC counts with the administration of *Carica Papaya* leaf juice in mice, and clinical studies by Siddique et al corroborated the same in humans.[9]

There were few adverse events reported related to GI disturbances like nausea, vomiting, hiccoughs and loose stools which were more in the study group than control group.[10]

Ethical approval: The study was approved by the Institutional Ethics Committee

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