



ORIGINAL RESEARCH PAPER

General Medicine

CARICA PAPAYA LEAF EXTRACT FOR TREATING THROMBOCYTOPENIA IN DENGUE FEVER- AN EXPERIENCE FROM A TERTIARY CARE CENTRE IN EASTERN PART OF INDIA

KEY WORDS: Carica papaya leaves, platelets, dengue fever

Dr Satish Kr. Prasad

M.D. Medicine, Senior Consultant, Department Of Medicine, Tata Main Hospital, Jamshedpur.

Dr. Sameer Kr. Mehta*

M.D. Medicine, Consultant, Department Of Medicine, Tata Main Hospital, Jamshedpur. *Corresponding Author

Ankit Poddar

D.N.B Medicine, Associate Specialist, Department Of Medicine, Tata Main Hospital, Jamshedpur.

ABSTRACT

Background: Dengue fever is the most common arboviral mosquito-borne tropical disease of humans caused by the dengue virus. The incidence has increased many fold in India due to unplanned urbanization and migration of population to urban areas. **Aim** -To study if Carica papaya leaf extract will significantly increase the platelet count in cases of thrombocytopenia associated with Dengue fever. **Materials and Methods-** The case control study was conducted in the Department of Medicine of Tata Main Hospital, Jamshedpur. All participants were randomised into two groups, study group (n=50) and control group (50); the study group was given papaya leaf extract capsule of 1100 mg thrice daily for five days but the control group did not receive it. The basic supportive treatment of dengue fever was provided to both the groups. **Results-** On the first day, platelet count of study group and control group was $(63.68 \pm 16.88$, and $57.07 \pm 17.46 \times 10^3$ respectively, p value=0.0573). The mean platelet count on Day 2, Day 3, Day 4 of CPC administration (mean \pm S.D) was $80.34 \pm 18.54 \times 10^3$, $104.14 \pm 20.42 \times 10^3$, $135.08 \pm 19.91 \times 10^3$ in the case group and $64.48 \pm 17.02 \times 10^3$, $77.02 \pm 16.88 \times 10^3$, $100.70 \pm 18.33 \times 10^3$ in the control group respectively. The mean duration of stay in the study group was 4.6 ± 0.67 days and 6.76 ± 1.54 days in the control group (p<0.01). **Conclusion-** Carica papaya leaves extract capsules offer a cheap and possibly effective treatment for increasing the platelet count in dengue.

INTRODUCTION

Dengue fever is the most common arboviral mosquito-borne tropical disease of humans caused by the dengue virus.¹ Dengue has become a global problem since the Second World War and is endemic in more than 110 countries.^{2,3} Each year between 50 and 100 million people are infected with approximately 10,000 to 20,000 deaths.^{4,5} The earliest descriptions of an outbreak date from 1779. Its viral cause and spread were understood by the early 20th century.⁶ The incidence has increased manifold in India due to unplanned urbanization and migration of population to urban areas. It is classified as a neglected tropical disease.⁷ It is the most common viral disease transmitted by arthropods, and has a disease burden estimated at 1,600 disability-adjusted life years per million population. The World Health Organization counts dengue as one of seventeen neglected tropical diseases.⁸

Symptoms typically begin three to fourteen days after infection. This may include a high fever, headache, vomiting, muscle and joint pains, and a characteristic skin rash.^{9,10} Recovery generally takes two to seven days. In a small proportion of cases, the disease develops into the life-threatening dengue haemorrhagic fever or into dengue shock syndrome.⁷

The management of dengue virus infection is essentially supportive and symptomatic. No specific treatment is available. Patients with severe thrombocytopenia and bleeding require platelet transfusion. A novel vaccine for dengue fever has been approved and is commercially available in many countries. Work is also ongoing for medication targeted directly at the virus.⁷ Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and corticosteroids should not be used.⁸ But till the time a drug is available, there is a need for alternative therapy that would decrease the morbidity and mortality.

Carica papaya leaf extracts is one such therapy that has been shown to increase the platelet count in Dengue fever in several studies. Carica papaya is a member of the Caricaceae

family. 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, and the West Indies. The papaya fruit is consumed in its fresh form, juice, and crystallized dry fruit¹⁰. The ripe fruit is a rich source of vitamin A, C, and calcium¹¹. C. papaya leaves have been used in folk medicine for centuries. The leaves of papaya have been shown to contain many active components such as papain, chymopapain, cystatine, tocopherol, ascorbic acid, flavonoids, cyanogenic glucosides and glucocynolates. Recent studies have shown it to be beneficial for its antitumor, immunomodulatory, anti-inflammatory, antioxidative and wound healing properties. 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-Hydroxyeicosatetraenoic acid (12-HETE) production of platelets¹². The PTAFR gene was been found to be expressed in megakaryocytes indicating that it could be a precursor for platelet production in addition to its role in platelet aggregation¹³. Carica papaya leaf extract increases the activity of ALOX 12 gene. Platelets may also show an increased reaction with leucocytes and endothelial cells, leading to their destruction.^{14,15} Platelet dysfunction due to abnormal activation and inhibition of platelet aggregation in dengue patients may also be responsible for the destruction.^{16,17} Increased levels of mediators like tumour necrosis factor- α and interleukin1 β were associated with thrombocytopenia.

Currently treatment strategy for thrombocytopenia in dengue is only platelet transfusion. The thrombocytopenia is not addressed till it gets lowered down to levels less than 10000 / μ l or bleeding manifestations are present irrespective of the platelet count, where platelet transfusion is advocated. Thrombopoietin receptor agonists like Eltrombopag and Romiplostim are available to increase the platelet counts,

however, cost and accessibility factors would hamper larger proportion of people from availing them and, they are associated with adverse effects. Therefore, in the current lieu, considerations for alternate therapies to combat the low platelet count, which is relatively free from the toxic side effects of the drugs, should be given.^{18,19}

Carica Papaya Leaf Extract in the management of thrombocytopenia associated with dengue is significant as it would be better & viable option in fever associated with thrombocytopenia, palatable and appropriately formulated, fewer side effects, cost effective and may decrease the morbidity. Therefore, this study was conducted in our hospital to see the effects of *Carica papaya* leaf extract on platelet count and to compare the duration of hospitalization between study and control groups.

MATERIAL AND METHODS:

The Study was conducted in the Department of Medicine of Tata Main Hospital, Jamshedpur, a century old tertiary care centre in eastern part of India. A total of 100 patients of Dengue fever with thrombocytopenia were included into the study which was done over a period of one and half years, from March 2017 to September 2018. It is a comparative study design (Case Control Study) with 50 patients each in the study group (cases) and the control group. The study group received a capsule (1100 mg) of *Carica papaya* leaf extract three times a day for five days. Whereas the control group did not receive it. The basic supportive treatment was provided to both the groups. Patients with age between 18 to 60 years, diagnosed dengue fever by the presence of NS-1 antigen, having platelet count between 30000 to 100000 per micro litre, AST and ALT levels less than 3 times the upper limit of normal and who gave prior informed consent to participate in the study were included in the study. The Exclusion criteria comprised of patients diagnosed with DHF Grade 3 or Grade 4, those with platelet count less than 30,000 per micro litre, pregnant or lactating women, patients who received blood or blood products transfusion during the current hospital stay or during last 1 month, patients diagnosed with ITP, Leukaemia, Haemophilia, patients with impaired renal function with serum creatinine level > 1.4 mg/dl (female) or >1.5 mg/dl (male), and AST or ALT level 3 times higher than the upper normal limit. The platelet counts and average hospital stay duration in both study and control groups were compared statistically by student t-test.

RESULTS

The present study was done on 100 patients of dengue with 50 patients (39 males and 19 females) in the study group who received carica papaya leaf extract capsule and 50 patients (29 males and 21 females) in the control group who did not receive it. The study showed that there was a faster and higher increase in platelet count in study group compared to control group.

On the first day platelet count of study group and control group was ($63.68 \pm 16.88 \times 10^3$, and $57.07 \pm 17.46 \times 10^3$ respectively, p value=0.0573). The mean platelet count on Day 2, Day 3, Day 4 of CPC administration (mean \pm s.d.) was $80.34 \pm 18.54 \times 10^3$, $104.14 \pm 20.42 \times 10^3$, $135.08 \pm 19.91 \times 10^3$ in the case group respectively and $64.48 \pm 17.02 \times 10^3$, $77.02 \pm 16.88 \times 10^3$, $100.70 \pm 18.33 \times 10^3$ in the control group respectively. Mean platelet count on Day 2, Day 3, Day 4 was significantly higher in the case group as compared to the control group (p<0.01) (figure 1) The mean duration of stay in the study group was 4.6 ± 0.67 days and 6.76 ± 1.54 days in the control group (p<0.01) (figure 2), This indicates that *Carica papaya* leaf extract tends to fasten the natural course of rate of platelet rise in dengue fever. Thus, in our study significant increase in the platelet count started to occur from day 2 of the institution of the carica papaya leaf extract capsule. No side effects of the capsule were recorded.

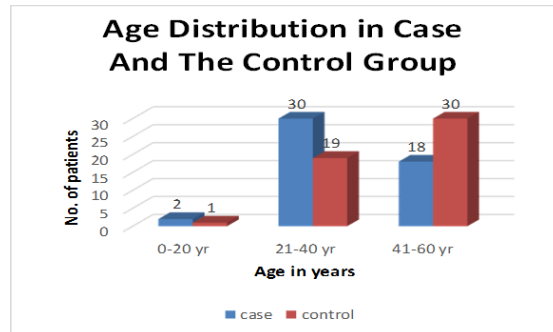


Figure 1-Age distribution

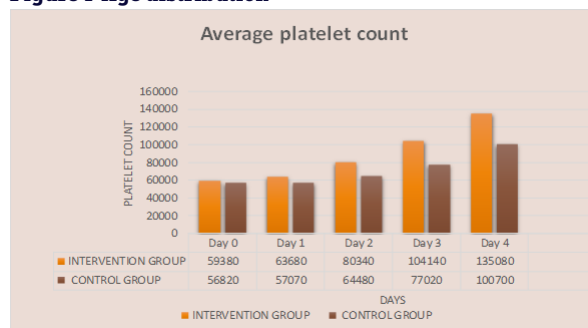


Figure 2-Mean Platelet Count

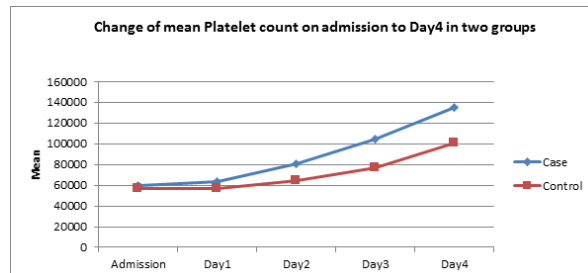
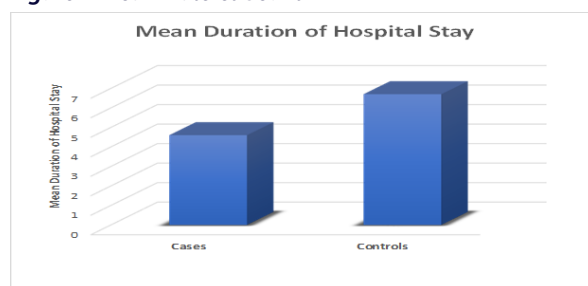


Figure 4-Increase in the mean Platelet Count from Admission to Day 4 in cases and controls

DISCUSSION

In a randomised double blind placebo controlled study by Adarsh et al. average platelet count was significantly (p < 0.01) higher in the group who received carica papaya leaf extract capsules on day 3,4 and 5. Also the duration of hospitalization in the intervention group was 3.45 ± 0.98 days and in the control group 6.42 ± 0.98 (p < 0.01) days. In the study done by Ajeet Kumar Gadhwale et al²⁰, the platelet count of study group was significantly higher on day3, 4 and 5. The platelet count of study and the control group were 82.96 ± 16.72 , and 66.45 ± 17.36 thousands respectively on day 3, 122.43 ± 19.36 and 112.47 ± 17.49 thousands respectively on day 4 and 88.75 ± 21.65 and 102.59 ± 19.35 thousands on day 5 (p value < 0.01). The average hospitalization period of study group v/s control group was 3.65 ± 0.97 v/s 5.42 ± 0.98 days, which was statistically significant (p value < 0.01). Similarly, in a randomised open label controlled study by Gowda et al²¹ in patients between 18 to 60 years, showed that at baseline, mean

Platelet Count was 64.79×10^3 among test group and 65.94×10^3 among control group and the difference was not statistically significant. Mean platelet count on day 5 in the intervention group was $104.71 \pm 30.57 \times 10^3$ and in the control group was $66.63 \pm 22.49 \times 10^3$. Mean difference in platelet count from day 1 to day 5 in the intervention group was $39.92 \pm 38.51 \times 10^3$ and in the control group was $00.69 \pm 24.75 \times 10^3$, ($p = 0003$). After the treatment at the end of Day 5, mean Platelet Count showed a significant increase of 61.6% in test group and an insignificant rise of 1.0% in control group from baseline. The difference was statistically significant. Nisar Ahmad et al²² in their study found that mean platelet count on day 1 to day 5 was significantly increase in dengue fever treatment with carica papaya leaves extract capsules.

In a study by Vijeth et al²³, significant increase in platelet count was seen in patients receiving CPLE on the third day onwards till the 5th day but from 6th day onwards platelet counts reduced in both groups. On admission mean platelet count of study group was 95247 where as in placebo group it was 98470

($p=0.971$). On 2nd day mean platelet counts of both the groups decreased to 94950 and 81141 respectively ($p=0.211$). But on third day among study group mean platelet count rose to 97270, where as in placebo group it was still 71663. The mean difference among these two groups was found significant ($p=0.002$). On 5th day, mean platelet count of study group and placebo group were 111936 and 78098 respectively ($p=0.04$). Overall it was found that Carica Papaya Leaf Extract tends to fasten the natural course of rate of platelet rise in dengue fever. When compared about the discharge rate among two groups, it was seen that discharge rate is earlier in study group. Results of our study were similar to the mentioned studies apart from the fact that in our study the platelet count started improving significantly from Day2 as compared to Day 3 in other studies. It may be hypothesised that the active components of CPLE such as papain, chymopapain, flavonoids, cystatin, tocopherol, ascorbic acid, and cyanogenic-glucosides inhibit immune mediated platelet destruction and bone marrow suppression by virus. Thus, it hastens the natural course of recovery with increase in the platelet count without any side effects.

TABLE 1-COPMARISION WITH VARIOUS STUDIES

| STUDY AND AUTHOR | TYPE OF STUDY | INCLUSION CRITERIA | INTERVENTION | RESULTS | SIDE EFFECTS |
|-------------------------------|--|---|---|---|----------------------------------|
| OUR STUDY (Prasad et al) 2019 | Case Control Study | Patients 18 to 60 years, diagnosed DF with platelet count between 30 to 100×10^9 (50 each patient in intervention and control group) | CP leaf extract tablets 1100 mg three times a day for five days | The mean platelet count on Day 2, Day 3, Day 4 of CPC administration (mean \pm s.d.) was $80.34 \pm 18.54 \times 10^3$, $104.14 \pm 20.42 \times 10^3$, $135.08 \pm 19.91 \times 10^3$ in the case group respectively and $64.48 \pm 17.02 \times 10^3$, $77.02 \pm 16.88 \times 10^3$, $100.70 \pm 18.33 \times 10^3$ in the control group respectively | Not reported |
| Gowda et al. 2015 | Randomized, open label controlled study | Patients 18–60 years with DF or DHF I, II with platelet count $30-100 \times 10^9$ (14 intervention group, 16 control group) | CP leaf extract tablets 1100 mg three times a day for five days | Mean platelet count on day 5: intervention group 104.71 ± 30.57 , control group 66.63 ± 22.49 . Mean difference in platelet count from day 1 to day 5: intervention group 39.92 ± 38.51 , control group 00.69 ± 24.75 , $p = 0003$. | Not reported |
| Gadhwal et al. 2016 | Randomized controlled study | Patients > 16 years with DF and platelet count $< 150 \times 10^9$ (200 in each group) | CP leaf extract capsule 500 mg once daily for five days | Mean platelet count was higher in the intervention group from 3rd to 5th day. Average hospitalization period: intervention group 3.65 ± 0.97 days, control group 5.42 ± 0.98 , $p < 0.01$. Platelet transfusion requirements: intervention group 55/200, control group 93/200. | No side effects reported with CP |
| Adarsh et al. 2017 | Randomized double blind placebo controlled study | Adult patients with DF (50 each) | CP leaf extract capsules 500 mg three times a day for five days | Average platelet count was higher in the intervention group on day 3, 4 and 5 ($p < 0.01$). Platelet transfusion requirements: intervention group 28%, control group 46% ($p < 0.01$). White cell count increased in the intervention group. Haematocrit did not show significant difference. Duration of hospitalization: intervention group 3.45 ± 0.98 , control group 6.42 ± 0.98 ($p < 0.01$). | Nausea, vomiting |
| Vijeth et al. 2018 | Randomized double blind placebo controlled study | Adult patients >18 years of age (127 males and 73 females). 100 patients in each group | CP leaf extract | There was an increase in platelet counts in study group compared to placebo group and on third day there was significant difference between both ($p=0.002$). The discharge was rate earlier in study group than placebo group. | No side effects reported |

CONCLUSION

Carica papaya leaves extract capsules offer a cheap and possibly effective treatment for dengue. It could be used as an additional drug in acute febrile illness patients with thrombocytopenia in dengue. It hastens the increase in the platelet count and shorten the hospitalization thereby reducing the cost of hospitalization significantly. Various

clinical and preclinical studies conducted have demonstrated a positive effect in dengue cases with thrombocytopenia. Realtime platelet values are not available at most of the places and there is time lag for reports to arrive during which there can be a further decline in the platelet count. Hence the recommendation for use of platelet increasing agent as a proactive measure. This comparative 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.

REFERENCES

1. Akram, W., Khan, H. A., Hafeez, F., Bilal, H., Kim, Y. K., & Lee, J. J. (2010). Potential of citrus seed extracts against dengue fever mosquito, *Aedes albopictus* (Skuse)(Culicidae:Diptera). *Pak/Bot*, 42(4), 3343-3348.
2. Ranjit, S., & Kisson, N. (2011). Dengue hemorrhagic fever and shock syndromes. *Pediatric Critical Care Medicine*, 12(1), 90-100.
3. Gubler, D. J. (1998). Dengue and dengue hemorrhagic fever. *Clinical microbiology reviews*, 11(3), 480-496.
4. Whitehorn, J., & Farrar, J. (2010). Dengue. *British medical bulletin*, 95(1), 161-173.
5. Stanaway, J. D., Shepard, D. S., Undurraga, E. A., Halasa, Y. A., Coffeng, L. E., Brady, O. J., ... & Murray, C. J. (2016). The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. *The Lancet infectious diseases*, 16(6), 712-723.
6. Henchal, E. A., & Putnak, J. R. (1990). The dengue viruses. *Clinical microbiology reviews*, 3(4), 376-396.
7. Noble, C. G., Chen, Y. L., Dong, H., et al. Strategies for development of Dengue virus inhibitors. *Antiviral Res.* 2010; 85(3): 450-62.
8. World Health Organization. (2013). Neglected tropical diseases: the 17 neglected tropical diseases.
9. Haagsma, J. A., De Noordhout, C. M., Polinder, S., Vos, T., Havelaar, A. H., Cassini, A., ... & Salomon, J. A. (2015). Assessing disability weights based on the responses of 30,660 people from four European countries. *Population health metrics*, 13(1), 1-15.
10. Gurung, S., & Škalco-Basnet, N. (2009). Wound healing properties of *Carica papaya* latex: in vivo evaluation in mice burn model. *Journal of Ethnopharmacology*, 121(2), 338-341.
11. Otsuki, N., Dang, N. H., Kumagai, E., Kondo, A., Iwata, S., & Morimoto, C. (2010). Aqueous extract of *Carica papaya* leaves exhibits anti-tumor activity and immunomodulatory effects. *Journal of ethnopharmacology*, 127(3), 760-767.
12. Subenthiran, S., Choon, T. C., Cheong, K. C., Thayyan, R., Teck, M. B., Muniandy, P. K., ... & Ismail, Z. (2013). *Carica papaya* leaves juice significantly accelerates the rate of increase in platelet count among patients with dengue fever and dengue haemorrhagic fever. *Evidence-Based Complementary and Alternative Medicine*, 2013.
13. Gadhwal, A. K., Ankit, B. S., Chahar, C., Tania, P., Sirohi, P., & Agrawal, R. P. (2016). Effect of *Carica papaya* leaf extract capsule on platelet count in patients of dengue fever with thrombocytopenia. *J Assoc Physicians India*, 64(6), 22-26.
14. Krishnamurti, C., Peat, R. A., Cutting, M. A., & Rothwell, S. W. (2002). Platelet adhesion to dengue-2 virus-infected endothelial cells. *The American journal of tropical medicine and hygiene*, 66(4), 435-441.
15. Akca, S., Haji-Michael, P., De Mendonça, A., Suter, P., Levi, M., & Vincent, J. L. (2002). Time course of platelet counts in critically ill patients. *Critical care medicine*, 30(4), 753-756.
16. Cines, D. B., & Blanchette, V. S. (2002). Immune thrombocytopenic purpura. *New England Journal of Medicine*, 346(13), 995-1008.
17. Noisakran, S., Chokephaibulkit, K., Songprakhon, P., Onlamoon, N., Hsiao, H. M., Villinger, F., & Perng, C. C. (2009). A re-evaluation of the mechanisms leading to dengue hemorrhagic fever. *Annals of the New York Academy of Sciences*, 1171, E24-E35.
18. Pentewar, R., Sharma, S., Kore, P., Kawdewar, D., & Somwanshi, S. (2017). *Papaya leaf extract to Treat dengue: a review. Sch. Acad. J. Pharm*, 6(4), 113-119.
19. Patil, S., Shetty, S., Bhide, R., & Narayanan, S. (2013). Evaluation of platelet augmentation activity of *Carica papaya* leaf aqueous extract in rats. *Journal of Pharmacognosy and phytochemistry*, 1(5).
20. Gadhwal, A. K., Ankit, B. S., Chahar, C., Tania, P., Sirohi, P., & Agrawal, R. P. (2016). Effect of *Carica papaya* leaf extract capsule on platelet count in patients of dengue fever with thrombocytopenia. *J Assoc Physicians India*, 64(6), 22-26.
21. Gowda, A. C., Kumar, N. V., Kasture, P. N., & Nagabhushan, K. H. (2015). 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*, 149, 109-16.
22. Ahmad, N., Fazal, H., Ayaz, M., Abbasi, B. H., Mohammad, I., & Fazal, L. (2011). Dengue fever treatment with *Carica papaya* leaves extracts. *Asian Pacific journal of tropical biomedicine*, 1(4), 330-333.
23. Vijeth, S. B., Kauser, M. M., Mangsuli, V., Kumar, V. S. R., Sree, S., & Varghese, S. A. (2018). Effect of *Carica papaya* leaf extract (CPL) on thrombocytopenia among dengue patients of tertiary care hospital, Chitradurga, India. *International journal of Advances in medicine*, 5(4), 974-977.