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Original Research Article

A Study on Investigating the role of Papaya Extracts in the Management of Acute Thrombocytopenia in Dengue Fever, is there any Clinical Significance?

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Abstract

Pakistan had an epidemic of dengue fever with a yearly prevalence of 0.4-0.5/100,000 reported. In the current epidemics of dengue, utilization of Carica papaya leaves earned popularity in treating thrombocytopenia.Our main objective was to determine the course and duration of recovery of thrombocytopenia in patients with dengue infection who were using papaya extracts and compare them to those who did not receive papaya extracts during the hospital stay. The study included all the patients with a diagnosis of dengue infection via serology, with the exclusion of all patients who were transfused with platelets during the hospital stay, or had a known chronic or autoimmune thrombocytopenic illness. ICU admissions and mortalities were also excluded from the study population. Platelet counts of study groups were monitored and compared at Day 1, 4 and 7 with one group using papaya extracts alongside intravenous hydration administered in both study and control groups. There was no significant difference in the length of hospital stay between the two groups, no added benefit in the doubling time of platelets. Although many studies are supporting the role of papaya extracts in increasing platelet counts on a molecular level, its role in attaining recovery from acute thrombocytopenic conditions like dengue viral fever is still ambiguous and lack clinical evidence in our study.

Keywords: Dengue fever, Disease control, Disease prevention, Public Health, Treatment

INTRODUCTION

Dengue is one of the most prevalent arthropod-borne infectious diseases propagated by Aedes mosquitoes (Stegomyia and Albopictus) (Vijeth et al., 2018; Yboa and Labrague, 2013; Gadhawal et al., 2016). Dengue fever is imparted by a group of tightly knitted serotypes DENV1, DENV2, DENV3 and DENV4 (Yboa and Labrague, 2013). It is a distinctive universal health problem with an approximation of 50-100 million infections globally (Gadhawal et al., 2016; Venugopal et al., 2018). Dengue has estimated epidemiology of involving 2.5 billion people all over the globe with 400 million infections yearly along with a mortality rate of 5-20% in endemic regions ((Kasture et al., 2016; Matysiak and Roess, 2017). Pakistan had an epidemic of dengue, getting victimized by serotypes DENV2, DENV3 infecting 23,000 people leading to hospitalization in 2011 and yearly prevalence of 0.4/100,000, 0.1/100,000 and 0.5/100,000 in 2013, 2014 and 2015 were recorded respectively (Javed et al., 2018; Suleman et al., 2017). Dengue is entitled as a neglected tropical disease (NTD) distressing poverty-stricken and deprived populations of the world with a poor standard of living (Matysiak and Roess, 2017). Dengue fever clinically manifests itself with flu-like symptoms along with the sudden onset of a painful headache, high spiking fever (103-106 degrees Fahrenheit), myalgia, arthralgia, retro-orbital pain, nausea, vomiting along with

generalized erythematous rash erupting 4-7 days after the mosquito bite and diminishing after 3- 10 days (Yboa and Labrague, 2013; Venugopal et al., 2018; Kasture et al., 2016; Matysiak and Roess, 2017; Ahmed et al., 2011). Dengue fever also manifests itself with bleeding gums, upper gastrointestinal bleed, hematuria if complicated by thrombocytopenia (Venugopal et al., 2018; Sarala and Panikar, 2014). Unusual presentation of dengue comprises encephalitis, hepatitis, myocarditis, and cholecystitis (Sarala and Panikar, 2014). Dengue fever has an incubation interval of 8-10 days (Matysiak and Roess, 2017; Srikanth et al., 2019). Initial presentation of infection projects within 5-7 days in normal person due to vector's bite (Kasture et al., 2016; Ahmed et al., 2011). AedesEgypti, the causative mosquito of dengue fever is female endemic in tropical and subtropical regions of the world having its sustenance on blood and reproducing on stale water in isolated containers and car tires (Matysiak and Roess, 2017; Cox et al., 2007). Pathology of dengue fever is associated with the destruction of the immune system by a viral attack involving humoral immunity and cell-mediated immunity resulting in the multiplication of T cells and the release of pro-inflammatory cytokines leading to vascular endothelial cell disorder and throm-bocytopenia causing capillary plasma leakage (Kasture et al., 2016; Kularatne, 2015; Stephenson, 2005). Several conditions accounting for thrombocytopenia in dengue include bone marrow suppression, platelet dysfunction, platelet lysis and disorientation of coagulation factors responsible for bleeding in dengue patients (Kasture et al., 2016; Kularatne, 2015; Sharma et al., 2019; Chinnappan et al., 2016). Laboratory outcomes of dengue fever are supportive of leucopenia, neutropenia and throm-bocytopenia in complete blood count (CBC) test, leucopenia coupled with positive tourniquet test is suggestive of dengue in prevalent areas, hematocrit levels spike is detected owing to lack of hydration, increase in levels of aspartate and alanine transaminases denote derangement of liver function tests. Detection of viral nucleic acid antigen (Dengue NS-1 antigen) and antibody (IgM) along with serology are confirmatory tests. Radiological investigations are conducted when dengue shock syndrome or dengue hemorrhagic fever are diagnosed, a lateral decubitus chest radiograph is advised to detect pleural effusion in the initial stage of plasma leakage and ultrasound abdomen is advised to detect ascites and plasma leak in abdominal viscera including liver, gall bladder and kidneys (Vijeth et al., 2018; Kularatne, 2015; Sawasdivorn et al., 2001; World Health Organization, Special Programme for Research and Training in Tropical Diseases (TDR), 2009). Dengue fever, if left untreated or inadequately treated, predis-poses to life-threatening complications such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) being more prevalent in children and unusual in adults. The mortality rate of 10-20% is recorded in people with untreated dengue hemorrhagic fever leading to excessive capillary permeability and thrombocytopenia culminating into dengue shock syndrome (DSS) than death (Yboa and Labrague, 2013; Sarala and Panikar, 2014; Kularatne, 2015; Petres, 2012; Teixeira and Barreto, 2009). Long term manifestation of dengue fever is rare but sufferer may develop post-viral fatigue syndrome, platelet levels slowly peak, liver function tests attain their normal levels in a period of 4 weeks (Kula-ratne, 2015; Teixeira and Barreto, 2009). Cornerstone treatment of dengue is intravenous hydration and supportive management (Venugopal et al., 2018; Ahmed et al., 2011; Kularatne, 2015). Acetaminophen is used to get relief from symptomatic fever. On contrast drugs like aspirin, NSAIDs, and steroids are to be avoided because they are notorious in triggering gastritis and bleeding (Ahmed et al., 2011; Kularatne, 2015). In recent times there is no definitive treatment of dengue, or prevention available in the form of the antiviral vaccine (Venugopal et al., 2018; Kasture et al., 2016; Sarala and Panikar, 2014; Kularatne, 2015).

In the current epidemics of dengue, utilization of Carica papaya leaves earned popularity due to their natural tendency of curing dengue among masses as herbal medication (Vijeth et al., 2018; Kala, 2012; Singhai et al., 2016). Carica papaya leaves potentially convey their therapeutic effect by managing thrombocytopenia, raising levels of leukocytes and platelets, sustain the normal levels of hematocrit, and presumptively minimizes the duration of hospital stay among dengue patients (Gadhawal et al., 2016; Sarala and Panikar, 2014; Srikanth et al., 2019; Yunita et al., 2012). Carica papaya leaves are composed of active ingredients that presumptively play a role in curing adverse conditions of dengue fever include papain, chymopapain, cystatin, L-tocopherol, ascorbic acid, flavonoids, cyanogenic, glucosides and glucosinolates (Gadhawal et al., 2016; Ahmed et al., 2011; Otsuki et al., 2010; Anjum et al., 2017). These compounds present in circa papaya leaves are mediators of anti-inflammatory, anti-tumor, and immunomodulatory activity exerted by circa papaya leaves (Gadhawal et al., 2016; Otsuki et al., 2010; Anjum et al., 2017; Owoyele et al., 2008). Carica papaya leaves are revealed to potentiate the manifestation of Arachidonate 12- lipoxygenase (ALOX) and platelet-activating factor receptor (PAFTR) gene, hence increasing the phenomenon of platelet production and aggregation (Venugopal et al., 2018; Srikanth et al., 2019; Kasture et al., 2016; Singhai et al., 2016; Suben-thiran et al., 2013; Dharmarathna et al., 2013). Although Carica papaya leaves are herbal medication, they are also responsible for countable adverse effects among consumers, few commonly encountered are nausea, vomiting, rash, itching, abdominal pain, hiccoughs and loose stools (Gadhawal et al., 2016; Venugopal et al., 2018; Kasture et al., 2016; Siddique et al., 2014; Ahmad et al., 2011; Senthilvel et al., 2013).

Our main objective was to determine the course and duration of recovery of thrombocytopenia in patients with dengue infection who were using papaya extracts and compare them to those who did not receive papaya extracts during the hospital stay.

MATERIALS, METHODOLOGY, AND STUDY DESIGN

This study was conducted at the Department of Medicine at Dow University Hospital Karachi, Pakistan; which is a 380-bed tertiary care hospital, receiving patients from almost all the states of the country. The study was designed as an observational, comparative survey during the latest epidemic of Dengue fever in the city of Karachi in October 2019.

The study included all the patients with a diagnosis of dengue infection either via Dengue NS-1 antigen or IgM antibody who had evidence of decreased platelets and febrile illness. All patients who were transfused with platelets during hospital stay were excluded from the study (n=47). Similarly, all patients who had known chronic liver disease or autoimmune illness (i.e, SLE, ITP) which can be an unambiguous factor in persistent thrombocytopenia, were excluded from the study population (n=6). While few patients were admitted in the Intensive care unit (n=12), which included mortalities (n=3), were also excluded from the study. The rest of the exclusions were due to loss of follow up after discharge (n=33). The final sample size of the study population calculated was 158, with each arm of 79 participants, calculated via W.H.O sample size calculator, type I error (alpha) = 0.07 and power of study of 90%. A non-probability consecutive sampling method was used to select the sample, with a focus to involve equal males and females in the study.

All patients included in the study were monitored with platelet counts every 12 hourly after admission. The platelet counts on day 1 of admission were recorded and compared between both groups, with group B receiving papaya extracts along with intravenous hydration (n=79) while the group A only receiving intravenous hydration (n=86). Subsequent platelet counts were monitored and compared between the two groups on day 4th and 7th from the initial day of admission, and also the length of hospital stay. All analysis was conducted by using the Statistical Package for Social Science (SPSS) version 25.0 (Armonk, NY, USA).

RESULTS

The medical records of 165 adult patients who were admitted to our hospital with a diagnosis of dengue infection during the months of October and early November 2019 were analyzed, who fulfilled our inclusion criteria. Dengue NS-1 was positive in 78.7% of the patients while the IgM antibody was positive in 21.2% (both simultaneously positive in 16.3%). The mean age of the study population was 33.56 ± 14.2 years. The demographic data of the study population extracted is shown in Table 1.

The mean platelet count on the day of admission was 31.41 ± 17.7 $x10^9$/L. The mean time to reach doubled platelet count from day 1 was 3.38 ± 1.52 days. The mean time required for platelets to double was 3.32 ± 1.29 days in group A (n=86) and 3.45 ± 1.73 days in group B (n=79). The mean platelet counts on day 4 and day 7 were also comparable in both groups respectively. There was no significant difference in the length of hospital stay between the two groups, and a comparison of mean platelet counts at different intervals is shown in Table 2.

The prognostic parameters such as length of hospital stay and platelet doubling time were also compared along with their degree of distribution among the study groups and concluded in statistical indifference. Hence, it was concluded that there was no clinically significant role of papaya extracts in the improvement of platelet counts and prognostic status of dengue patients in our study, as shown in Figure 1.

DISCUSSION

Education and comprehension of dengue fever among the public are reviewed crucial in developing the ability to opt prophylactic actions against it (Yboa and Labrague, 2013; Javed et al., 2018; Baksh et al., 2018; Wong et al., 2015; Zaki et al., 2019; Nguyen et al., 2019; Handel et al., 2016). Electronic coverage in the form of television, radio, internet, and newspaper plays a vital role in creating consciousness regarding dengue fever and its prevention thus promoting awareness campaigns (Javed et al., 2018; Baksh et al., 2018; Nguyen et al., 2019; Smith et al., 2016; Vo and Pham, 2018). Lack of education, awareness, effective methods of communication, obligations to implement prophylactic measures among public and misconceptions regarding transmission, etiology and treatment and prevention of dengue fever are the culprit of rendering dengue endemic in affected areas (Matysiak and Roess, 2017; Javed et al., 2018; Baksh et al., 2018; Wong et al., 2015; Nguyen et al., 2019; Handel et al., 2016; Vo and Pham, 2018; Itrat et al., 2008). Government institutions, non-government institutions, health care providers and social media reform agencies need to focus on developing the foundation of educational campaigns, health care facilities, pamphlets, internet awareness, and radio transmissions to impart knowledge about dengue fever and it's treatment, prevention, and etiology among students, patients, and the local public to eradicate dengue in endemic areas (Yboa and Labrague, 2013; Javed et al., 2018; Nguyen et al., 2019; Handel et al.,

Table 1. showing demographic data of the study population

#	Variables	Values	p-value
1	Mean age in years	33.56 ± 14.21	0.039*
	Males (n=85)	31.35 ±13.40	
	Females (n=80)	35.92 ±14.74	
2	Confirmation of diagnosis	NS-1 antigen positive: 130 (78.78%)	0.636**
		IgM antibody positive: 35 (21.21%)	
		Both simultaneously positive: 27 (16.36%)	
3	Mean Platelet count at Day 1	31.41 ±17.72	-
4	Mean Platelet count at Day 4	82.30 ±33.39	-
5	Mean Platelet count at Day 7	224.13 ±97.40	-
6	Mean days of Hospital stay	4.04 ±1.15	-
	95% confidence interval	3.87-4.22	-
	Median	4.00	-
	Interquartile range (IQR)	3.00-4.00	-
7	Mean Platelet doubling time from Day 1 (in days)	3.38 ±1.52	-
	95% confidence interval	3.15-3.62	-
	Median	3.00	-
	Interquartile range (IQR)	2.50-4.00	-

Descriptive statistics are presented either as Mean ± SD or median and IQR.
Frequencies are presented as n(%), where n= number of subjects.
**indicates independent sample t-test used to compute the p-value.*
*** indicates chi-square test to compute the p-value.*
Abbreviations: IQR, interquartile range; SD, standard deviation; NS-1, non-structural protein-1.

Table 2. Showing comparative statistics amongst the control and study groups.

#	Frequencies	Group A (n=86)	Group B (n=79)	p-value
1	Mean Age in years	31.34 ± 13.54)	35.99 ± 14.62	0.036*
2	Male count (n=85)	43	42	0.685**
3	Female count (n=80)	43	37	
4	Mean Platelet count at Day 1	27.85 ± 12.38	35.29 ± 21.54	0.008*
5	Mean Platelet count at Day 4	83.79 ± 31.88	80.70 ± 35.09	0.554*
6	Mean Platelet count at Day 7	217.23 ± 92.10)	231.64 ± 102.92	0.344*
7	Mean days of Hospital stay	4.07 ± 1.17	4.02 ± 1.14	0.805*
	95% confidence interval	3.81-4.31	3.76-4.28	0.852†
	Median	4.00	4.00	
	Interquartile range (IQR)	1.00	1.00	
	Mean rank of hospital stay	83.63	82.32	
8	Mean Platelet doubling time from Day 1 (in days)	3.32 ± 1.29	3.45 ± 1.73	0.584*
	95% confidence interval	3.04-3.60	3.06-3.84	0.744†
	Median	3.00	3.00	
	Interquartile range (IQR)	1.50	2.50	
	Mean rank of platelet doubling time	84.15	81.75	

Descriptive statistics are presented either as Mean ± SD or median and IQR.
Frequencies are presented as n = no. of subjects.
** indicates independent sample t-test, ** indicates Chi-square test, † indicates Mann Whitney U-test.*
Abbreviations: IQR, interquartile range; SD, standard deviation.

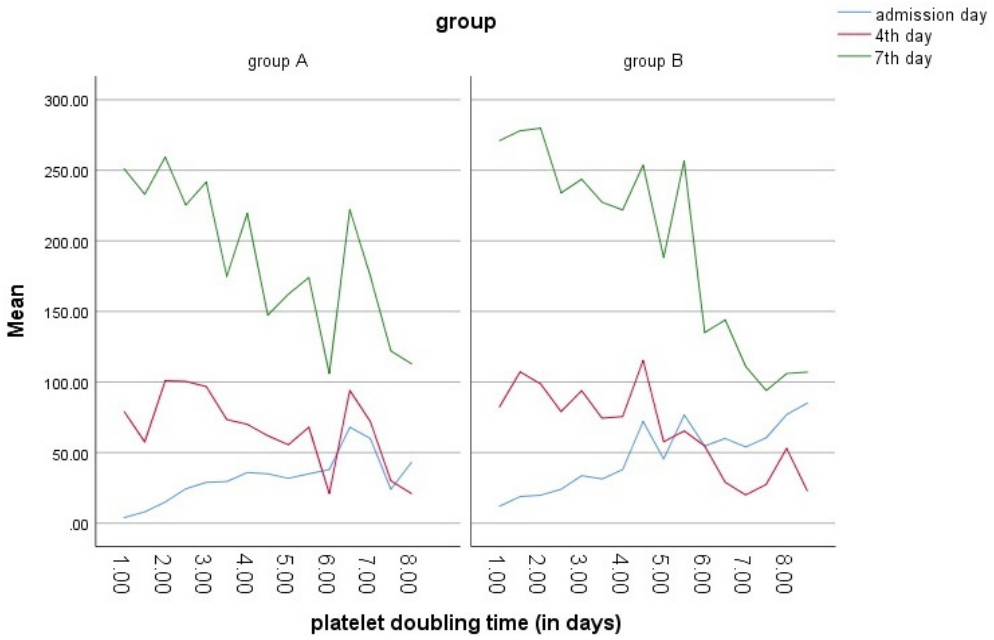

Figure 1. Showing trends of platelet counts in the study groups with respect to the length of the hospital stay.

2016; Itrat et al., 2008; Alayousefi et al., 2016).

There is no definitive cure available for dengue fever and appropriate supportive measures in the form of Intravenous hydration and symptomatic modalities are cornerstone management. Application of circa papaya leaves extract in order to cure thrombocytopenia, as the main manifestation of dengue, is cited by many studies (Vijeth et al., 2018; Venugopal et al., 2018; Kasture et al., 2016; Singhai et al., 2016; Otsuki et al., 2010; Subenthiran et al., 2013; Dharmarathna et al., 2013), but due to the ambiguity of scientific evidence, it cannot be considered authentic. Our study observed the effects of circa papaya leave on a variety of manifestations of dengue, especially thrombocytopenia, by evaluating platelet doubling time from admission to the length hospital stay, and monitoring of platelets at 4th and 7th day of hospitalization to attain normal levels. The results showing that there is no significant clinical evidence of using circa papaya leaves in attaining recovery from acute thrombocytopenic conditions like dengue viral fever (Sarala and Panikar, 2014; Sharma and Mishra, 2014).

CONCLUSION

There was no significant difference in the course and recovery time of platelet counts in patients who were using papaya extracts versus the patients who were on intravenous hydration. The length of hospital stay also remains unaffected in both study groups. The purpose of the study was to identify one of the psychosocial factors affecting dengue prognosis. Many patients donot take urgent medical care with active dengue infection and thrombocytopenia due to the popular belief in the society that papaya leaves are the cure of this disease. Such patients hence develop bleeding during the disease course, which sometimes involves a major organ and leads to mortality. The most important part of dengue management remains intravenous and oral hydration and keeping the hematocrit levels normal with minimization of plasma leakage, hence avoiding complications. Althoughmany studies are supporting the role of papaya extracts in increasing platelet counts on a molecular level in a longer period (Gadhawal et al., 2016; Sarala and Panikar, 2014; Srikanth et al., 2019; Kala, 2012; Yunita et al., 2012; Anjum et al., 2017; Owoyele et al., 2008), its role in attaining recovery from acute thrombocytopenic conditions like dengue viral fever is still ambiguous and lack clinical evidence in our study. We conclude that there was no clinically significant added benefit of papaya extracts between the two groups treated with intravenous hydration. The authorities need to create awareness in the masses regarding the misbeliefs revolving around dengue management so that we can properly manage this disease (Baksh et al., 2018; Nguyen et al., 2019; Smith et al., 2016; Itrat et al., 2008).

Conflicts of Interests

The authors declare no conflicts of interest withthe article's content.

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Ethical Approval Statement

Ethical approval was taken in this study from the institutional review board, and consent to participate has been taken from all the patient's guardians with informed written consent.

REFERENCES

Ahmad N, Fazal H, Ayaz M, et al. (2011). Dengue fever treatment with Carica papaya leaves extracts. Asian Pac J Trop Biomed. 1:330-333.

Ahmed N, Fazal H, Ayaz M, Abbasi BH, Muhammad I, Fazal H (2011). Dengue fever treatment with Carica papaya leaves extract. Asian pacific journal of biomedicine. 1(4):330-333. DOI:10.1016 /S2221-1691(11)60055-5

Alayousefi TAA, Ghani RA, Mahdy MAK, Al- Eryani SMA, Al-Melkhlafi AM, Raja YA, Shah SA, et al. (2016). A household-based survey of knowledge, attitudes and practices towards dengue fever among local urban communities in Taiz Governorate, Yemen. BMC infectious diseases. 16(543):1-9. DOI: 10.1186/s12879-016-1895-2

Anjum V, Arora P, Ansari SH, Najmi AK, Ahmad S (2017). Antithrombocytopenic and immunomodulatory potential of metabolically characterized aqueous extract of Carica papaya leaves. Pharmaceutical biology. 55(1):2043-2056. DOI: 10.1080/13880209.2017.1346690

Baksh K, Sana F, Ahmad N (2018). Dengue fever in Punjab, Pakistan: Knowledge, perception and adaptation among urban adults. Elsevier B.V. Science of total environment. 6(44):1304-1311. DOI: https://doi.org/10.1016/j.scitotenv.2018.07.077

Chinnappan S, Kothanuru VKS, Ramachandrappa, Tamilrasu K, Krishnan UM, Pillai AKB, et al (2016). Inhibition of platelet aggregation by the leaf extrac of Carica papaya during dengue infection: An in vitro study. Viral Immunology. 29(3):1-5. DOI: 10.1089/vim.2015.0083

Cox J, Grillet ME, Ramos OM, Amador M, Barrera R (2007). Habitat segregation of dengue vectors along an urban environmental gradient. American journal of tropical medicine and hygiene. 76(5):820-826.

Dharmarathna SL, Wickramasinghe S, Waduge RN, Rajapakse RP, Kularatne SA (2013). Does Carica papaya leaf-extract increase the platelet count? An experimental study in a murine model. Asian Pac J Trop Biomed. 3(9):720-724.

Gadhawal AK, Ankit BS, Chahar C, Tantia P, Sirohi P, Agarwal RP (2016). Effect of Carica papaya leaf extract capsule on platelet count in patients of dengue fever with thrombocytopenia. Journal of the Association of physicians of India. 64:22-26. DOI: https://www.researchgate.net/publication/304886198. PMID: 277 39263

Handel AS, Ayala EB, Cordova MJB, Fessler AG, Finkelstein JL, Espinoza RXR, et al. (2016). Knowledge, attitudes, and practices regarding dengue infection among public sector healthcare providers in Machala, Ecuador. Biomed central. Tropical diseases, travel medicine and vaccines. 2(8):1-10. DOI: 10.1186/s40794-016-0024-y

Itrat A, Khan A, Javaid S, Kamal M, Khan H, Javed S, et al. (2008). Knowledge, Awareness and Practices Regarding Dengue Fever among the Adult Population of Dengue Hit Cosmopolitan. PLoS ONE. 3(7):e2620. DOI: 10.1371/journal.pone.0002620

Javed N, Ghazanfar H, Naseem S (2018). Knowledge of dengue among students exposed to various awareness campaigns in model schools of Islamabad: A cross-sectional study. Cureus. 10(4). DOI: 10.7759/cureus.2455

Kala CP (2012). Leaf Juice of Carica papaya L: A Remedy of Dengue Fever. Med Aromat Plants. 1:109. doi:10. 4172/2167-0412. 1000109

Kasture PN, Nagabhushan KH, Kumar A (2016). A multi-centric, double-blind, placebo-controlled, randomized, prospective study to evaluate the efficacy and safety of Carica papaya leaf extract, as empirical therapy for thrombocytopenia associated with dengue fever. Journal of the Association of physicians of India. 64: 15-20.

Kularatne SAM (2015). Dengue fever. The Bmj. 3(51):1-10. DOI: 10.1136/bmj.h4661

Matysiak A, Roess A (2017). Interrelationship between climatic, ecologic, social and cultural determinants affecting dengue emergence and transmission in Puerto Rico and their implications for Zika response. Hindawi J. Trop. Med. 1-14. DOI: https://doi.org/10.1155/2017/8947067

Nguyen PV, Vo TQ, Nguyen TD, Phan TTC, Phan NVH (2019). Dengue fever in Southern of Vietnam: A survey of reported knowledge, attitudes, and practices. Health economics and community-oriented practice in Vietnam. 69(6):118-129.

Otsuki N, Dang NH, Kumagai E, Kondo A, Iwata S, Morimoto C (2010). Aqueous extract of Carica papaya leaves exhibits anti-tumor activity and immunomodulatory effects. J Ethnopharmacology. 127:760-767.

Owoyele BV, Adebukola OM, Funmilayo AA, Soladoye AO (2008). Anti-inflammatory activities of ethanolic extract of Carica papaya leaves. Inflammopharmacology 16:168-173.

Petres CJ (2012). Infections caused by arthropod and rodent borne viruses. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrisons Principles of Internal Medicine. 18th edition. New York: McGraw Hill, Medical Publishing Division; 1617-33.

Sarala N, Panikar SS (2014). Papaya extract to treat dengue: A novel therapeutic option. Annals of medical and health sciences research. 4(3):320-324.

Sawasdivorn S, Vibulvattanakit S, Sasavatpakdee M, et al. (2001). Efficacy of clinical diagnosis of dengue fever in paediatric age groups as determined by WHO case definition 1997 in Thailand. Dengue Bull. 25:56-64.

Senthilvel P, Lavanya P, Kumar KM, Swetha R, Anitha P, Bag S, et al. (2013). Flavonoid from Carica papaya inhibits NS2B-NS3 protease and prevents Dengue 2 viral assembly. Bioinformation. 9(18):889.

Sharma N, Mishra D (2014). Papaya leaves in dengue fever: Is there scientific evidence. Correspondence Indian pediatrics. 51:324-325.

Sharma N, Mishra KP, Chanda S, Bhardawaj V, Tanwar H, Ganju L, et al. (2019). Evaluation of anti-dengue activity of Carica papaya leaf extract and its role in platelet augmentation. Archives of Virology. 164(4):1095-1110. PMID: 30790105. DOI: https:// doi.org/10.1007/s00705-019-04179-z

Siddique O, Sundus A, Ibrahim MF (2014). Effects of Papaya Leaves on thrombocyte counts in dengue. J Pak Med Assoc. 64(3):364-366.

Singhai A, Juneja V, Abbas S, Jha RK (2016). The effect of Carica papaya leaves extract capsules on platelets count and hematocrit

levels in acute febrile illness with thrombocytopenia patient. International journal of medical research & health sciences, 5(1):254-257.

Smith AW, Cohn E, Lloyd DC, Tozan Y, Brownstein JS (2016). Internet-based media coverage on dengue in Sri Lanka between 2007 and 2015. Global health action. 9(31):1-5. DOI: http://dx.doi.org/10.3402/gha.v9.31620

Srikanth BK, Reddy L, Biradar S, Shamanna M, Mariguddi DD, Kumar MK (2019). An open-label, randomized prospective study to evaluate the efficacy and safety of Carica papaya leaf extract for thrombocytopenia associated with dengue fever in pediatric subjects. Dovepress medical health journal, pediatric health, medicine and therapeutics. 10:5-11.

Stephenson JR (2005). Understanding dengue pathogenesis: implication for vaccine design. Bull World Health Organ. 83:308-314.

Subenthiran S, Choon TC, Cheong KC, et al. (2013). Carica papaya leaves juice significantly accelerates the rate of increase in platelet count among patients with dengue fever, dengue haemorrhagic fever. Evidence Based Complement Alternat Med. 616-737. PMID: 23662145. DOI: 10.1155/2013/616737

Suleman M, Faryal R, Alam MM, Sharif S, Shaukat S, Aamir UB, et al. (2017). Dengue virus serotypes circulating in Khyber Pakhtunkhwa province, Pakistan, 2013-2015. Annals of laboratory medicine. 37:151-154. DOI: https://doi.org/10.3343/alm.2017.37.2.151

Teixeira MG, Barreto M (2009). Diagnosis and management of dengue: clinical review. BMJ. 3(39):1189-93.

Venugopal K, Suresh RM, Haleshah BR (2018). Role of Carica papaya leaf extract tablets/capsules on platelet count in cases of dengue thrombocytopenia. Int. J. Adv. Med. 5(4): 845-848. DOI: http://dx.doi.org/10.18203/2349-3933.ijam20182500

Vijeth SB, Kauser MM, Mangsuli V, Kumar VSR, Sree S, Varghese SA (2018). Effect of Carica papaya leaf extract (CPLE) on thrombocytopenia among dengue patients of tertiary care hospital, Chitradurga, India. International journal of Advances in medicine. 5(4):974-977. DOI: http://dx.doi.org/10.18203/2349-3933.ijam20183131

Vo TQ, Pham TTP (2018). Revisiting dengue-related knowledge, attitudes and practices: A cross-sectional study in Ho Chi Minh City, Vietnam, Health economics and community-oriented practice in Vietnam. 2019; 69(6):108-117.

Wong LP, Shakir SMM, Atefi N, AbuBakar S (2015). Factors Affecting Dengue Prevention Practices: Nationwide Survey of the Malaysian Public. PLoS ONE. 10(4):e0122890. DOI:10.1371/journal.pone.0122890

World Health Organization, Special Programme for Research and Training in Tropical Diseases (TDR) (2009). Dengue guidelines for diagnosis, treatment, prevention and control: new edition. http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf?ua=1.

Yboa BC, Labrague LJ (2013). Dengue knowledge and preventive practices among rural residents in Samar province, Philippines. Ame. J. Pub. Health Res. 1(2): 47-52. DOI:10.12691/ajphr-1-2-2

Yunita F, Endang, Hanani, Kristianto J (2012). Effect of carica papaya Leaves extract capsules on platelet count and hematocrit in dengue patient. Int J MedArom Plants. 2:573-578.

Zaki R, Roffeei SN, Hii YL, Yahya A, Appannan M, Said MA, et al. (2019). Public perception and attitude towards dengue prevention activity and response to dengue early warning in Malaysia. PLoS ONE. 14(2):e0212497. DOI: https://doi.org/10.1371/journal.pone.0212497

Table 1. showing demographic data of the study population

#	Variables	Values	p-value
1	Mean age in years	33.56 ± 14.21	0.039*
	Males (n=85)	31.35 ±13.40	
	Females (n=80)	35.92 ±14.74	
2	Confirmation of diagnosis	NS-1 antigen positive: 130 (78.78%)	0.636**
		IgM antibody positive: 35 (21.21%)	
		Both simultaneously positive: 27 (16.36%)	
3	Mean Platelet count at Day 1	31.41 ±17.72	-
4	Mean Platelet count at Day 4	82.30 ±33.39	-
5	Mean Platelet count at Day 7	224.13 ±97.40	-
6	Mean days of Hospital stay	4.04 ±1.15	-
	95% confidence interval	3.87-4.22	-
	Median	4.00	-
	Interquartile range (IQR)	3.00-4.00	-
7	Mean Platelet doubling time from Day 1 (in days)	3.38 ±1.52	-
	95% confidence interval	3.15-3.62	-
	Median	3.00	-
	Interquartile range (IQR)	2.50-4.00	-

Descriptive statistics are presented either as Mean ± SD or median and IQR.
Frequencies are presented as n(%), where n= number of subjects.
**indicates independent sample t-test used to compute the p-value.*
*** indicates chi-square test to compute the p-value.*
Abbreviations: IQR, interquartile range; SD, standard deviation; NS-1, non-structural protein-1.

Table 2. Showing comparative statistics amongst the control and study groups.

#	Frequencies	Group A (n=86)	Group B (n=79)	p-value
1	Mean Age in years	31.34 ± 13.54)	35.99 ± 14.62	0.036*
2	Male count (n=85)	43	42	0.685**
3	Female count (n=80)	43	37	
4	Mean Platelet count at Day 1	27.85 ± 12.38	35.29 ± 21.54	0.008*
5	Mean Platelet count at Day 4	83.79 ± 31.88	80.70 ± 35.09	0.554*
6	Mean Platelet count at Day 7	217.23 ± 92.10)	231.64 ± 102.92	0.344*
7	Mean days of Hospital stay	4.07 ± 1.17	4.02 ± 1.14	0.805*
	95% confidence interval	3.81-4.31	3.76-4.28	0.852†
	Median	4.00	4.00	
	Interquartile range (IQR)	1.00	1.00	
	Mean rank of hospital stay	83.63	82.32	
8	Mean Platelet doubling time from Day 1 (in days)	3.32 ± 1.29	3.45 ± 1.73	0.584*
	95% confidence interval	3.04-3.60	3.06-3.84	0.744†
	Median	3.00	3.00	
	Interquartile range (IQR)	1.50	2.50	
	Mean rank of platelet doubling time	84.15	81.75	

Descriptive statistics are presented either as Mean ± SD or median and IQR.
Frequencies are presented as n = no. of subjects.
** indicates independent sample t-test, ** indicates Chi-square test, † indicates Mann Whitney U-test.*
Abbreviations: IQR, interquartile range; SD, standard deviation.

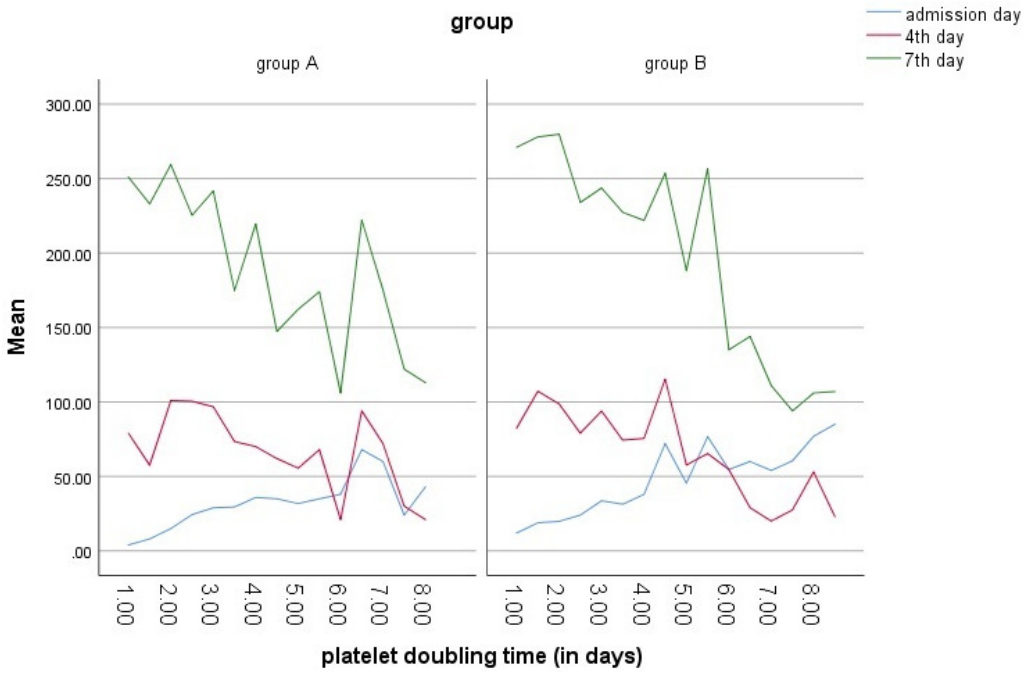

Figure 1. Showing trends of platelet counts in the study groups with respect to the length of the hospital stay.