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Effect of Carica Papaya Leaves Juice on Duration of Hospital Stay among Children with Dengue Fever and Dengue Haemorrhagic Fever

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Abstract

Background: Over the last 10-15 years, dengue fever (DF) and dengue hemorrhagic fever (DHF) have become the leading causes of hospitalization and death among both children and adult. *Carica papaya* leaves juice is said to increase platelet count, reduce complication and duration of Hospital stay. ***Objective:*** This study aimed to determine the effect of *Carica papaya* leaf juice on duration of Hospital stay in child patients with DF and DHF. ***Methods:*** This randomized controlled trial was conducted among 77 children with DF and DHF. Patients were purposively selected from the inpatient department of Dhaka Shishu hospital from July 2018 to December 2019. Patients were randomly allocated in group A and group B. Group A patients received standard treatment along with a bottle containing *C. papaya* leaves juice 10 ml single morning dose 15 minutes after breakfast for three consecutive days and group B patients received only standard management as per the National Guideline for Clinical Management of Dengue Syndrome, 2018. Three patients in group A and two patients in group B dropped out from the study. ***Results:*** There was no significant difference between the groups regarding age, sex, mean duration, type and severity of fever between the groups ($p>.05$). In group A, the mean platelet count increased from 105000.00/ mL to 152428.57/mL after 48 hours and it reached to 212228.57/mL at 72hrs. In group B, the mean platelet count initially decreased from 129485.71/ mL to 91114.28/mL after 48 hours and then it increased to 96142.85/mL at 72 hours. There was highly significant statistical difference between group A and group B at 48 hours and at 72 hours regarding mean platelet count as p <0.001. Haematocrit values become significantly normal in group A than group B by 72 hours and p value <0.05. There was highly significant statistical difference between group A and group B regarding mean hospital stay as p <0.001. ***Conclusion:*** Administration of *Carica papaya* leaf juice shorten hospitalization in patients with Dengue fever and Dengue haemorrhagic fever.

Keywords: Dengue fever, Dengue Haemorrhagic Fever, *Carica papaya* leaf juice,Paediatric patients.

INTRODUCTION

Dengue is caused by a virus of the Flaviviridae family and there are four distinct, but closely related, serotypes of the virus that cause dengue (DENV-1, DENV-2, DENV- 3 and DENV-4). Dengue virus is transmitted by female mosquitoes mainly of the species *Aedes aegypti* and, to a lesser extent, *Ae. albopictus*. These mosquitoes are also vectors of chikungunya, yellow fever and Zika viruses. Dengue is widespread throughout the tropics, with local variations in risk influenced by rainfall, temperature, relative humidity and unplanned rapid urbanization [29].

In Bangladesh, the first epidemic of dengue haemorrhagic fever occurred in mid-2000 when 5,551 dengue infections were reported from Dhaka, Chattogram and Khulna. According to WHO, the worst

outbreak occurred in 2002, with 6,232 cases identified. Over the last 10-15 years, dengue fever and dengue haemorrhagic fever have become the leading causes of hospitalization and death among both children and adult in south-east Asian regions [21].

There is no specific antiviral drug available for the treatment of dengue infection. Infected patients receive supportive management with fluids, blood and blood products based on National Guideline for Clinical Management of Dengue Syndrome, 2018. Infection with homologous serotype is known to induce a life-long protective immunity to the homologous serotype but confers only partial and transient protection against subsequent infection by the other serotypes. Secondary infection is a major risk factor for DHF possibly due to antibody-dependent enhancement (ADE) [21].

Dengue causes a wide spectrum of disease. This can range from subclinical disease to severe flu-like symptoms in those infected. Although less common, some people develop severe dengue, which can be any number of complications associated with severe bleeding, organ impairment and/or plasma leakage. Severe dengue has a higher risk of death when not managed appropriately [29].

Headache, nausea, loss of appetite and bleeding diathesis are significant symptoms in dengue patients. There is some diversity in the Complete Blood Count in the dengue patients compared to healthy person. Dengue patients have higher hemoglobin and haematocrit from day 3 to day 10, lower white blood cell count from day 2 to day 10, lower platelet count from day 3 to day 10, higher monocyte on day 1– 4, higher atypical lymphocyte percentage on day 5– 9 and higher eosinophil percentage on day 9– 10 [7].

WHO estimates that in many countries 80% of the rural patients seek alternative treatment using medicinal plants. *Carica papaya* is a member of the Caricaceae and is a dicotyledonous, polygamous, and diploid species. *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, anti tumour as well as immune modulatory effects and as an antioxidant. Safety studies based on OECD (Organization for Economic Co-operation and Development) guideline for acute, sub- acute and chronic toxicity were conducted on *C. papaya* extract and showed that it was found to be safe for human consumption [3,12-13,16,22-23].

Carica papaya leaves juice helps in dengue by stimulation of haematopoietic system which stimulates platelet production, stimulates the immune system which enhances the activity against the viral infections, direct antiviral activity on dengue virus, it prevents chemically induced capillary leakage, speedy recovery with reduce hospitalization [10,24-25,30].

Some of the genes have shown to influence platelet production, namely, arachidonate 12-lipoxygenase (ALOX 12) and platelet-activating factor receptor (PTAFR). An upsurge in the activity of these genes is necessary for platelet production and activation. The ALOX 12 gene is intensely expressed in megakaryocytes, and it has shown to be accountable for the 12-hydroxyeicosatetraenoic acid (12-HETE) production of platelets in patients treated with CPLE extract. On megakaryocytes, PTAFR gene is expressed, which indicates that it might be a precursor for platelet production. Clinical evidence shows that C. papaya extract enhances the PTFAR activity around 13-fold and the ALOX 12 activity 15-fold, which is responsible for increased platelet production [28].

This study was conducted to determine the effect of *Carica papaya* leaf juice on duration of Hospital stay in child patients with DF and DHF.

MATERIALS AND METHODS

Plant Material and Sample Preparation: C. papaya leaves were collected from medicinal plant garden of Horticulture department, Sher-e-Bangla Agricultural University, Dhaka to ensure same authenticated source. The papaya trees of horticulture garden were kept free of herbicides, pesticides, and insecticides. Mature healthy leaves were collected from fruit bearing *Carica papaya* tree. Juice prepared within 6 hours of removing the leaf from the tree. All the necessary equipments should be cleaned before the procedure. Papaya leaves thoroughly washed for five times with running tap water then remove all the main stems of the leaves using a scissor, leaves washed once again. Leaves are cut into pieces and wash it well with boiled cool water and weight about 50g of papaya leaves and put it into a grinder and make a paste then add 50mL boiled cold water and 25g of sugar with the paste and grind well till a uniform pulp is formed. Keep the pulp about 30 minutes in rest. Use a sieve (avoid cotton sieve) and squeeze this pulp by hand to get the papaya leaf extract**,** 10ml of juice extract into each clean bottle and seal it by capping. This preparation should be used freshly or within 24 hours (If need refrigerated in +4˚ C). Bottle must shake well before the preparation is given.

This randomized controlled trial was conducted in Dhaka Shishu (Children) Hospital among the patients diagnosed with Dengue fever from July 2018-December 2019. A total of 80 patients with confirm diagnosis as DF or DHF aged between 03 years to 16 years with platelet count above 30000/mm^3 were initially enrolled in the study.

Among them 77 patients fulfilled the selection criteria. Dengue patients with waring sign like

abdominal pain or tenderness, persistent vomiting, evidence of clinical fluid accumulation, lethargy, restlessness or diagnosed as severe dengue, patients who received blood or blood product transfusion within last one month, diagnosed case of ITP, leukemia, hemophilia, Serum creatinine more than 1.2 mg/dl were excluded from the study.

Clinical diagnosis of Dengue Fever (DF) and Dengue haemorrhagic fever (DHF) were made by the clinician based on patient's' presentation and confirmed by blood investigations. All subjects were confirmed dengue by NS1 antigen positive or anti dengue IgM or IgG for Dengue or both positive. Once a current dengue infection confirmed, a thorough screening of the patients were conducted. Baseline investigations included Complete blood count (CBC), ALT and S. creatinine were done. During study period, regular clinical follow up was given according to guideline. The purpose, procedure, importance and benefit of the study were explained to the parents and informed written consent was taken. After taking informed written consent from parents of the selected patients, they were randomly allocated into two groups.

Group A patients received standard dengue treatment along with a bottle containing *C. papaya* leaves juice 10 ml single morning dose 15 minutes after breakfast for three consecutive days [15,28]. In group B, patients received the standard management as per the National Guideline for Clinical Management of Dengue Syndrome, 2018.

Patients were followed up with CBC reports 24 hourly for three consecutive days. Patients were clinically evaluated daily by the researcher. They were also evaluated specifically about any adverse effects related to study medications in both groups. Out of the 77 patients, one patient in group A took DORB and two patients did not receive the second dose of *C. papaya* leaves juice. In group B, two patients in group B took DORB. Finally, 72 patients completed the follow up schedule.

RESULTS

In Table I group A (51.4%) patients were male and in group B(54.1%) patients were male. Chi-square test showed that there was no significant difference between the groups regarding sex as p=0.631. Again, in group A, the mean age of the patients was 7.27 ± 2.71 years and in group B, the mean age of the patients was 7.54 ± 2.88 years.

Independent Sample t test showed that there was no significant difference between the groups regarding age as *p*= .683.

In Table II group A (67.7%) patients had Dengue haemorrhagic fever (DHF) and in group B, (62.2%) patients had Dengue haemorrhagic fever (DHF). Again, in group A (60.0%) patients had fever with warning sign and in group B (54.1%) patients had fever with warning sign. Chi-square test showed that there was no significant difference between the groups regarding characteristics of fever as *p*=0.629. The mean duration of fever of the patients was 3.43 ± 1.22 days and in group B, the mean duration of fever of the patients was 3.48 ± 1.15 days. Independent Sample t test showed that there was no significant difference between the groups regarding mean duration of fever as *p*=0.841.

Table III showed there was no significant statistical difference between group A and group B at baseline and at 24 hours regarding mean platelet count as *p*>0.05 (Independent Sample t test). There was highly significant statistical difference between group A and group B at 48 hours and at 72 hours regarding mean platelet count as *p*<.001(Independent Sample t test).

Table IV shows that there was no significant statistical difference between group A and group B at baseline and at 24 hours regarding mean haematocrit as p>0.05 (Independent Sample t test). There was significant statistical difference between group A and group B at 48 hours and at 72 hours regarding mean haematocrit as p< 0.05(Independent Sample t test).

Table V shows that patients of group A had 4.14 (± 0.43) days of Hospital stay while patients of group B had 6.00 (± 1.51) days of Hospital stay. Independent Sample t test showed that there was highly significant statistical difference between group A and group B regarding mean Hospital stay as p<0.001.

Table I: Comparison of patients by demographic characteristics

Demographic characteristics	Group A (n=35)	Group B (n=37)	*p* value
Sex			
Male	18 (51.4%)	20 (54.1%)	.631^{ns}
Female	17 (48.6%)	17 (45.9%)	
Age (in years) (Mean± SD)	7.27 ± 2.71	7.54 ±2.88	.683^{ns}

ns= not significant

Group A: Patient receives Standard dengue treatment along with *C. papaya* leaf juice

Group B: Patient receives only Standard dengue treatment

Table II: Comparison of patients by clinical characteristics

Clinical characteristics	Group A (n=35) No. (%)	Group B (n=37) No. (%)	*p* value
Clinical diagnosis			
Dengue fever (DF)	12 (34.3)	14 (37.8)	.803^{ns}
Dengue haemorrhagic fever (DHF)	23 (67.7)	23 (62.2)	
Warning sign			
Dengue Fever without warning sign	14 (40.0)	17 (45.9)	.629^{ns}
Dengue Fever with warning sign	21 (60.0)	20 (54.1)	
Duration of fever (in days) (Mean ± SD)	3.43 ± 1.22	3.48 ±1.15	.841^{ns}

ns= Not significant

Table III: Comparison of patients by mean Platelet count

Platelet count	Group A (n=35)	Group B (n=37)	*p* value
Baseline	105000.00±64096.89	129485.71±70144.96	.132^{ns}
At 24 hours	97171.43± 48097.62	119000.00±73105.08	.145^{ns}
At 48 hours	152428.57±42232.05	91114.28±53419.96	<.001**
At 72 hours	212228.57±42821.16	96142.85±41720.83	<.001**

** Highly significant
ns= Not significant

Table IV: Comparison of patients by mean haematocrit

Haematocrit	Group A (n=35)	Group B (n=37)	*p* value
Baseline	**39.32±2.78**	**38.17±3.77**	***.153^{ns}***
At 24 hours	**38.59± 2.59**	**39.79±3.75**	***.100^{ns}***
At 48 hours	**37.62± 2.37**	**39.46±2.59**	***.002****
At 72 hours	**36.93± 2.06**	**38.63±3.56**	***.018****

* Significant
ns= Not significant

Table V: Comparison of patients by hospital stay

Hospital stays (in days)	Group A (n=35) f (%)	Group B (n=37) f (%)	*p* value
4	31 (88.6)	4 (10.8)	
5	3 (8.6)	11 (29.7%)	
>5	1 (2.9)	22 (59.5)	
Mean ± SD	4.14 ± 0.43	6.00 ±1.51	< .001**

** Highly significant

DISCUSSION

Dengue is a mosquito-borne infection it has become a major international public health problem in recent decades. Papaya (*Carica papaya*) leaf extract has haemostatic and other medicinal properties [5,17]. Further, recent research revealed the beneficial effects of papaya leaf extract in Asian patients who have dengue haemorrhagic fever [1]. The present randomized controlled trial aimed to determine the effect of *Carica papaya* leaf juice on duration of hospital stay. A total of 80 children with Dengue fever and Dengue haemorrhagic fever were enrolled in the study where 77 patients fulfilled the selection criteria and randomly allocated into group A (n=38) and group B (n=39). However, one patient in group A and two patients in group B took DORB on 2nd day of admission. Again, one patient in group A refused to take the juice on the second day due to unpleasant taste. Thus, the total dropout number was 5 which were around 7%. Finally, 35 patients from group A and 37 patients from group B had complete the follow up schedule. Hence, the results of 72 patients were discussed in this chapter.

The mean age of the patients was near about 7 years in both groups. This result was consistent with the findings of Srikanth *et al.,* (2019) who conducted a study to assess the efficacy and safety of *Carica papaya* leaf extract in patients with thrombocytopenia associated with Dengue haemorrhagic fever.

In both groups proportion of male children were more which was similar to results of Srikanth *et al.,* (2019) and Yunita *et al.,* (2012).

The mean duration of fever of the patients in both groups was near about 3 days where there was no significant difference between the groups regarding mean duration of fever. Majority of the patient in both groups had Dengue haemorrhagic fever (DHF) had fever with warning sign. As this was a hospital-based study, the proportion of patients with fever with warning sign was more.

Dengue is generally a self-limiting disease and the disease induced thrombocytopenia usually reverses itself after taking a slight dip during the phase of defervescence. However, a significant number of patients succumb to the disease during the thrombocytopenic period [28]. After administration of papaya leaves juice in patients, the platelet count increased significantly more in group A from day 2 compared to group B ($p<.001$). Study of Srikanth, *et al.,* (2019) also reported similar findings in pediatric patients. Moreover, they found positive impact of *Carica papaya* leaf extract on RBC and WBC counts in pediatric patients. The pilot study of Hettige (2008) reported that platelet counts had increased in all patients within 24 hours after administering papaya leaf juice. The total white blood cell count was also elevated and patients were recovered without hospitalization. The case report of Ahmad *et al.,* (2011) reported that *Carica papaya* leaves aqueous extract exhibited potential activity against Dengue fever by increasing not only platelet count but also white blood cell count and neutrophil count. The randomized controlled clinical trial of Yunita *et al.,* (2012) showed that the capsule of *Carica papaya* leaves extract significantly increased platelet count. Studies conducted in adult patients with dengue have shown that *Carica papaya* leaves extract had significant increase in the platelet count over the therapy duration, in DF patients, confirming that *Carica papaya* leaves extract accelerates the increase in platelet count compared to the control group [18]. The randomized controlled clinical trial of Subenthiran *et al.,* (2013) also showed that the *Carica papaya* leaves extract juice significantly increased platelet count. They stated that the Platelet Activating Factor Receptor (PTAFR) gene which is known to be responsible for increased platelet production and aggregation was expressed 13.42- folds among the patients who consumed the juice as compared to the control group indicating that the juice had played an important role in addressing the arresting of bleeding tendencies among these patients. Senthilvel *et al.,* (2013) revealed that the flavonoid quercetin in *Carica papaya* might exert its antiviral activity by blocking the viral assembly mechanism of DENV2 virus.

Significant decrease of mean haematocrit percentage towards normal was observed in group A compared to group B at 48 hours and at 72 hours. This decreased mean haematocrit percentage towards normal value indicated the improvement of plasma leakage in group A. This was not observed in group B. This result was consistent with the study of Yunita *et al.,* (2012) which showed that the capsule of Carica papaya leaves extract significant change in haematocrit.

The mean hospital stay of the patients of group A was significantly less compared to group B. Only one patient in group A had hospital stay > 5 days while 22 patients in group B had hospital stay > 5 days. As *Carica papaya* leaves inpcreased in the platelet count faster in group A than group B, patients of group A were discharged from the hospital quickly. Yunita *et al.,* (2012) reported that the capsule of *Carica papaya* leaves shortened hospitalization.

Carica papaya leaf juice was well tolerated by the patients. Few patients complained of nausea and two patients had vomiting which were self-limiting.

CONCLUSION

The study result can be concluded that the administration of Carica papaya leaf juice shortens hospital stay in patients with Dengue fever and Dengue haemorrhagic fever.

Limitations of the study

- Patients below the age of 3 years and above 16 years were excluded from the study. Recruiting this age group would have been showed more generalized result for pediatric population.
- Single centered, results might not represent the entire population.
- The study place and population was selected purposively which might result in selection bias.

Recommendations

A large multicentre randomized controlled trial with long time follow-up can be done to see the benefit of *Carica papaya* leaves juice in dengue fever and thereby to incorporate it in the management schedule of patients with Dengue fever and Dengue haemorrhagic fever.

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