ORIGINAL ARTICLE

MANAGEMENT OF THROMBOCYTOPENIA AND FLU-LIKE SYMPTOMS IN DENGUE PATIENTS WITH HERBAL WATER OF *EUPHORBIA HIRTA*

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Background: Incidence of dengue increased 30 fold between 1960 and 2010. This increase is believed to be due to a combination of urbanisation, population growth, increased international travel, and global warming. We tried to find out the effect of herbal water of Tawa-tawa, also called *Euphorbia hirta*, on the flu like symptoms and blood parameters especially on thrombocytopenia. **Methods:** Total 125 patients with confirmed dengue fever admitted in medical ward of Sir Ganga Ram Hospital Lahore were included in this experimental study. Duration of study was 3 months. Patients were divided into 2 groups, i.e., group A (ages between 30 to 55 years) and group B (ages between 14 to 25 years). A blood sample was obtained on the day of enrolment and after 24 hours of using Tawa-tawa. The variables used were platelet count, haematocrit (HCT), WBC count, serum AST, ALT, IgM/IgG. **Results:** In men, platelet count was <25,000 and in women, it was >50,000. Haematocrit were >40% in men and 30–40% in women. TLC in a range of 4,000–11,000/mm^3 was observed in both males and females. IgM 'haemagglutination' antibody titres (>1:160) was observed in 71.3% females and 50% males. Serum AST was >40 IU/L in 38% females and 36% males. Serum ALT was >40 IU/L in 9.5% females and 12% males. In both group A and B platelet count and TLC were increased non-significantly after herbal water of *Euphorbia hirta* (*E. Hirta*). Haematocrit value decreased non-significantly after using the herbal water. Over 70% of patients showed moderate increase in their platelet count. However leucopoenia improved significantly after the use of aqueous extract of *E. hirta*. A marked recovery in fever and flu like symptoms was observed. **Conclusion:** In over 70% patients there was improvement in platelet count, TLC, fever, and flue-like symptoms.

Keywords: Dengue, Thrombocytopenia, *Euphorbia hirta*, Management

INTRODUCTION

Dengue fever also known as break bone fever caused by a virus Aedes aegypti. It is by far the most important arboviral pathogen in the tropics around the world, putting nearly one third of the global human population at risk of infection.[1] Dengue is endemic in more than 110 countries. It infects 50 to 100 million people per year worldwide leading to half a million hospitalisations, and approximately 12,500–25,000 deaths. The incidence of dengue has dramatically increased 30 fold between 1960 and 2010. This increase is believed to be due to a combination of urbanisation, population growth, increased international travel, and global warming.[2] The geographical distribution is all around the equator with 70% of the total 2.5 billion people living in the endemic areas from Asia and the Pacific.[3] In Pakistan it was an undiagnosed fever. Now the incidence of dengue in Pakistan is 48.7% and is increasing since 1994.[4]

Dengue fever is a painful, debilitating mosquito-borne disease caused by any one of four closely related dengue viruses. These viruses are related to the viruses that cause West Nile infection and yellow fever. Dengue fever is transmitted by the bite of an Aedes mosquito infected with dengue virus.

Dengue can also be transmitted via infected blood products, through organ donation, from mother to child during pregnancy or at birth.[5] The binding of a virus to a host cell is a first and critical stage in the infectious process and the mechanism and identity of cellular proteins involved in this process remains largely unknown.[6]

Once inside the skin, the virus genome is replicated in endoplasmic reticulum of Langerhans cells and produces new viral proteins and new viruses are released.[7] Virus enters white blood cells, and reproduces inside the cells. The white blood cells respond by producing interferon. This interferon is responsible for symptoms like fever, flu-like symptoms, and severe pain. Interferon also activates the adaptive immune system, which leads to the generation of antibodies against the virus and stimulates the killer T cells that directly attacks the virus infected cells. These antibodies bind closely to the viral proteins and target them for phagocytosis.[8]

Dengue haemorrhagic fever presents in two phases: an initial phase, which is characterised by sudden onset of fever and flu- like symptoms.[9] In severe infection, organs like liver and bone marrow can also be affected. Dysfunction of the bone marrow leads to reduced numbers of platelets, thus increasing the risk of

bleeding; causing major complication of dengue fever.[10] The result is high fever or hemorrhagic fever. Bleeding or loss of blood platelets and RBC. Within a week, a patient may die, if left untreated.[4] In the province of Punjab, most people are suffering due to an outbreak taking the shape of an epidemic of the dengue virus causing fear and sufferings in people.

Medical science has no remedy or vaccine to alleviate the situation so far. Treatment of acute dengue is supportive, using either oral or intravenous rehydration for mild or moderate disease, and intravenous fluids and blood transfusion for more severe cases. Dengue mosquito is God's creation, and so is the plant weed Tawa-tawa. No specific drug has been discovered to kill the dengue virus. Thus, medical profession relies only on the supportive measures to strengthen the body to recover from the disease. It is advised to drink lots of water, monitor TLC, HCT and Platelet count frequently. Use of anti-ulcer medicines, soft and easily digestible foods is advised. In addition, the patient is asked to avoid eating dark coloured foods to monitor the stool sample for color.[5,11]

Managing thrombocytopenia or low platelet count is a key to the patients' survival. For ages, native American tribes have been using a weed species, *Euphorbia hirta linn*, commonly called Tawa-tawa to treat dengue. It is reported to contain alkenes, triterpenes, phytosterols, tannins, polyphenols, and flavonoids.[12] Tawa-tawa, apparently, doesn't directly kill the dengue virus. But it has immunomodulatory activity.[13] It acts by promoting the development of blood platelets, stops haemorrhage and prevents further bleeding. It also improves the nausea and abdominal cramps. This herbal treatment makes the effects of dengue virus more bearable to the patient and hastens recovery.[14]

The present study was conducted to find out the effect of herbal water of Tawa-tawa on the flu-like symptoms and blood biochemical parameters, especially its effect on thrombocytopenia.

MATERIAL AND METHODS

This was an experimental study carried out at Sir Ganga Ram Hospital, Lahore Pakistan, during the epidemic of dengue fever from Aug to Oct of 2011. The study was approved by Fatima Jinnah Medical College's Ethical Committee. An informed consent was obtained from all the patients who agreed to participate in the study. Total 125 patients (55 women and 70 men) with confirmed dengue fever admitted in medical ward were included in the study. These patients were categorised into dengue fever and dengue hemorrhagic fever according to the WHO severity grading scale (Dean *et al* 2006). Patients were divided into 2 groups, i.e., group A (Mean age 53.89±10.94 years), and group B (Mean age 26.38±6.55 years). Blood sample was obtained on the day of enrolment and later after 24 hours of administration of dose of Tawa-tawa. The variables used were platelet count, haematocrit, WBC count, serum AST, ALT, estimated by Auto analyser. Serological assays of IgM/IgG were carried out by ELISA. All patients with a platelet count <50,000 were included for analysis. IgM haemagglutination antibody titres >1:160 for dengue type 2 were interpreted as positive result. All other cases of acute febrile illness, without any clinical features or haematological abnormalities of dengue fever, were excluded.

Data were analysed using SPSS-11. Clinical laboratory data on the day of presentation and after using the Tawa-tawa water for 24 hours was used to study the effects of herbal water. Student's *t*-test was applied to see any significant mean differences.

RESULTS

Group A included 20 male and 34 females aged 30–55 (Mean 53.89±1094) year. Group B included 50 males and 21 females aged 14–25 (Mean 26.38±6.55) years.

In group A, <25,000 platelet count was observed in 17.6% female and 65% males. Platelet count in a range of 25,000–50,000 was observed in 17.6% female and 25% males. Platelet count >50,000 was observed in 44% female and 45% male patients. Haematocrit was >40% in 26.4% female and 75% male patients. The value of haematocrit between 30–40% was noted in 53% female and 15% males. HCT <30% was observed in 11.7% females only. Total leukocyte count was <4,000/mm^3 in 17.65% females and 40% males. TLC in a range of 4,000–11,000/mm^3 was observed in 24% females and 65% males. TLC >11,000/mm^3 was observed in 23.5% females and 45% males. IgM haemagglutination antibody titres (>1:160) was observed 44% females and 50% males. Serum AST was >40 IU/L in 85% females and 29% males. Serum ALT was >40 IU/L in 20.6% females and 65% males (Table-1).

In group B, platelet count <25,000 was observed in 4.74% female and 40% males. Platelet count in a range of 25,000–50,000 was observed in 14.3% female and 22% males. Platelet count >50,000 was observed in 81% female and 34% male patients. Values of haematocrit were >40% in 42.8% female and 62% male patients. Haematocrit between 30% and 40% was noted in 52.3% female and 26% males. HCT <30% was observed in 9.5% females and 8% males. Total leukocyte count was <4,000/mm^3 in 4.72% females and 16% males. TLC in a range of 4,000–11,000/mm^3 was observed in 62% females and 40% males. TLC >11,000/mm^3 was observed in 9.5% females and 20% males. IgM haemagglutination antibody titres (>1:160) was observed 71.3% females and 50% males. Serum AST was >40 IU/L in 38% females and 36% males. Serum ALT was >40 IU/L in 9.5% females and 12% males (Table-1).

In group A, the platelet count before using herbal water was 29,000±25,288 and after herbal water it was 41,145±29,000. Haematocrit value was 45.19±9.99% before using the herbal water and afterwards it was 43.38±5.24%. TLC was 3,500±250 before and after using herbal water it was 4,700±180.

In group B platelet count before using herbal water was 28,909±1,566 and after herbal water it was 31,153±23,518. Haematocrit value was 47.09±6.68% before using the herbal water and after it was 45.51±3.01%. TLC before use of herbal water was 4,400±200/mm^3 while after using herbal water was 5,010±210/mm^3 (Table-2).

Table-1: Laboratory Investigations

Investigation	Group A (20 M) (34 F)	%	Group B (50 M) (21 F)	%
Platelet count/mm^3				
< 25,000	13 (M) 6 (F)	65 17.6	1 (F) 20 (M)	4.75 40
25,000-50,000	5 (M) 6 (F)	25 17.6	3 (F) 11 (M)	14.3 22.0
> 50,000	15 (F) 9 (M)	44 45	17 (F) 17 (M)	81 34
Haematocrit (%)				
>40	15 (M) 9 (F)	75 26.4	9 (F) 31 (M)	42.8 62
30–40	3 (M) 18 (F)	15 53	11 (F) 13 (M)	52.3 26
<30	0 (M) 4 (F)	00 11.7	2 (F) 4 (M)	9.5 8
Total leukocyte count/mm^3				
<4,000	8 (M) 6 (F)	40 17.65	1 (F) 8 (M)	4.76 16
4,000–11,000	13 (M) 8 (F)	65 24	13 (F) 20 (M)	62 40
>11,000	9 (M) 8 (F)	45 23.5	2 (F) 10 (M)	9.5 20
IgM hemagglutination antibody titres (>1:160)	15 (F) 10 (M)	44 50	25 (M) 15 (F)	50 71.3
Liver function tests **				
Serum asparate transaminase (>40 IU/L)	17 (M) 10 (F)	85 29	18 (M) 8 (F)	36 38
Serum alanine transaminase (>40 IU/L)	13 (M) 7 (F)	65 20.6	6 (M) 2 (F)	12 9.5

Table-2: Blood parameters before and after Tawa-tawa (Mean±SD)

Age group	Platelets Before	Platelets After	Haematocrit Before (%)	Haematocrit After (%)	TLC Before (/mm^3)	TLC After (/mm^3)
Group A 53.89±10.94	29,000 ±25,288	41,145* ±29,000	45.19 ±9.99	43.38 ±5.24	3500 ±250	4700 ±190
Group B 26.38±6.55	28,909 ±1566	31,153 ±23,518	47.09 ±6.68	45.51 ±3.01	4400 ±200	5010 ±210

*p<0.05= Significant

DISCUSSION

In modern medicine, plants occupy a very important place as the raw material for some important drugs. Synthetic drugs are effective in controlling different diseases but these are out of reach of millions of people. It is estimated that around 70,000 plant species have been used for medicinal purposes. The herbs provide the basic initial material for synthesis of conventional drugs.[15] Dengue virus is now endemic in Pakistan, circulating throughout the year with a peak incidence in the post-monsoon period.[16]

Younger patients in our study with age of <25 years were more susceptible to disease than patients with age >25 years. Our study is in line with a Pakistani study which also observed that the median age of dengue patients has decreased and younger patients may be more susceptible.[16]

A study found that dengue patients had low platelet count of <50,000/mm^3 during the acute phase of illness.[17] The present study indicates a marked thrombocytopenia with a platelet count <25,000/mm^3 in patients. However, another study found a count of 160,200/mm^3 during the acute phase.[8]

Haematocrit was found to be more than 40% in 42.8% female and 62% male patients. A similar study also observed HCT >40%.[8] Among 52.3% female and 26% males the value of haematocrit was found to be between 30–40%. HCT <30% was observed in 9.5% females and 8% males.

Total leukocyte count (TLC) was <4,000/mm^3 in 4.72% females and 16% males. TLC in a range of 4,000–11,000/mm^3 was observed in 62% females and 40% males. On the other hand, TLC >11,000/mm^3 was observed in 9.5% females and 20% males. Other similar studies also observed WBC <4,000/mm^3 in dengue patients.[18,19] It is reported that total and differential leukocyte counts may help to identify patients at risk of haemorrhage.[16]

A IgM haemagglutination antibody titre >1:160 was observed in 71.3% females and 50% males. The presence of IgM and IgG antibodies to dengue was demonstrated in 11% patients.[20]

In our study, werum AST level was >40 IU/L in both groups. According to another study deranged coagulation profile and SGPT ≥40 IU were predictive of dengue shock.[19] Elevated alanine aminotransferase level ≥70 IU/L was also reported for dengue fever.

The initial clinical and laboratory assessment can help in selecting appropriate investigations and empiric treatments for patients with imported fever.[18] A study reported that high viral load and intense activation of the immune system are associated with dengue hemorrhagic fever.[21] Spontaneous bleeding was observed in 17 (8%) patients and was associated with increased serum alanine and aspartate aminotransferase levels and lower median platelet counts. A secondary immune response was significantly associated with spontaneous bleeding and other severe clinical manifestations.[17,22]

Our study is in line with a study which observed that most abnormal WBC or platelet values were found between 3 and 6 days after the onset of symptoms, whereas most abnormal AST, ALT values were often found later on. High IgG levels are indicative of secondary infections.[17]

In both groups the platelet count and TLC were increased while HCT was decreased after use of herbal water. This study also observed that flu-like symptoms were markedly reduced after the intake of Tawa-tawa. Our finding is confirmed by number of studies which reported that *E. hirta* is used in the treatment of bronchial and respiratory diseases (asthma, bronchitis, hay fever etc.), and in conjunctivitis. The aqueous extract exhibits anxiolytic, analgesic, antipyretic, and anti-inflammatory activities.[23–27] It has antimicrobial activity specific to enteropathogens.[13] It has a 45% immuno-modulation activity by way of inhibition of nitric oxide production.[13,25] Flavanoids, a constituent of plant, have also been reported to be responsible for producing anti-inflammatory and humoral antibody responses.[26] The anti-inflammatory activity of *E. hirta* could be attributed to its ability to stabilise mast cell membrane, thereby inhibiting the release of inflammatory mediators.[27]

Our study is subject to some limitations. Our study enrolled patients only during the initial 72 hours of illness, these algorithms may not adequately reflect clinical practice outside of research setting where many patients came for medical attention after the first 72 hours of illness. Further validation using data-sets from additional prospective cohort studies conducted in other dengue endemic regions is needed to establish the clinical utility of our algorithms in other populations.

CONCLUSION

Majority of patients had improvement in their platelet count and leucopoenia after use of aqueous extract of *Euphorbia hirta*. A marked recovery in fever and flu-like symptoms was also observed. However, further research on the herbal treatment with *E. hirta* should be conducted in other dengue endemic regions to establish its clinical utility in management of dengue fever.

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