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To Study The Effectiveness Of Eupatorium Perfoliatum In Management Of Acute Dengue Fever, In Adult Population; A 3 Armed Comparative Clinical Trial.

1) Swati Sirsat, intern, Dhanvantari Homeopathic Medical College and Hospital & Research hospital , Nashik
2) Zainab Mazarbhuiya, intern, Dhanvantari homeopathic medical college and hospital & Research hospital , Nashik
3) Dr. Mahesh Manshani. HOD department of Organon of Medicine , Dhanvantari homeopathic medical college and hospital & Research hospital ,Nashik
4) Dr. Snehal Kapadnis, Asst. Professor department of Repertory, Dhanvantari homeopathic medical college and hospital & Research hospital , Nashik
5) Dr. Gulfisha Mirza, Asst. Professor department of Surgery, Dhanvantari Homeopathic Medical College and hospital & Research hospital , Nashik
6) Dr. Mohit Jain, Asst. Professor department of Pharmacy, Dhanvantari Homeopathic Medical College and hospital & Research hospital , Nashik

ABSTRACT

1. . **Study Design**

A three armed clinical trial is a clinical research experiment in which a new proposed treatment is compared against existing standard form of treatment. It consists of 'Control group' which continues with the homoeopathy treatment. 'Experimental group' which receives allopathic treatment with homeopathic medicines. An 'Observational group' which is given the allopathic treatment.

In this study we shall be comparing the effects of homoeopathic medicine. Eupatorium perfoliatum in dengue fever of adult population with a Experimental group of individual taking antiviral medications and other allopathic drugs according to symptomatology –TAMIFLU, AZTREONAM AND CEFACTIVE for viral fever

Keywords:

Dengue Fever, Adult Population, Eupatorium Perfoliatum, Clinical Trail, Etc.

2. Operational Definitions:

Dengue fever is mosquito borne infections, transmitted by Aedes aegypti,clinically manifested as High/low grade fever(pattern classically biphasic or saddleback & breaking), Rash(maculopapular) ,Thromboctopaenia, Myalgia , Arthralgia and Gastrointestinal symptoms like nausea & vomiting and lasting for 3-14 days(Incubation Period).

The study will be carried out on adults suffering from Dengue fever based on Dengue Severity Scale.

Out of 30 cases, 10 cases are under allopathic treatment and 10 cases will be given homoeopathic medicine with allopathic medicine to assess its effects and remaining 10 cases will receive pure homeopathic medicine Eupatorium perfoliatum.

Result:

Out of 30 cases, 10 are homoeopathic cases, in which 8 cases got improved and 2 cases did not improve. Next 10 cases are of allopathic, in which 6 cases get improved with allopathic treatment and 4 cases did not improve. The last 10 cases are allopathic cases intervention with homoeopathic cases, in which 5 cases get improved with both Pathy treatment and 5 cases did not get improved. Maximum patients belonged to the age group 30 -80 years of age; 7 patients belonged to the age group of 15 -30 years of age, 23 patients belonged to 30 – 80 years of age. Around 60 percent of patients were male and 40 percents were female.

Conclusion:

Cases in which homeopathic medicine is prescribed, the result are quick and faster in relief of complaints.

INTRODUCTION

DEFINITION – Dengue fever, also known as break bone fever, is a mosquito-borne, virus disease characterized by fever, headache, myalgia, and arthralgia, and often an exanthema. Dengue is the most prevalent mosquito-borne viral disease in people.1

CAUSATIVE FACTOR: It is caused by four dengue virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4), of the genus Flavivirus, and transmitted by Aedes aegypti mosquitoes. 2

RATIONALE OF DISEASE

- Approximately 1 million cases of dengue, a major cause of morbidity in tropical and sub-tropical regions, are reported annually to the World Health Organization (WHO).
- The 2009 revised WHO dengue case classification for the diagnosis and management of the illness follows previous guidelines published by World Health Organization between 1974 and 1997.
    - This article investigates the clinical application of the 1997 and 2009 criteria to the reporting and management of dengue and difficulties of using the classification schemes.

KNOWLEDGE GAP

- Dengue virus is a mosquito-borne pathogen that causes up to about 100 million cases of disease each year, placing a major public health, social, and economic burden on numerous low-income and middle-income countries.
- Major advances by investigators, vaccine developers, and affected communities are revealing new insights and enabling novel interventions and approaches to dengue prevention and control.
- In this report, we approached to dengue diagnostics, disease prognosis, surveillance, and vector control in low-income and middle-income countries, as well as potential consequences of vaccine introduction.

Through this research we hope to increase awareness and remove the complications of dengue fever and assess the efficacy of Eupatorium Perfoliatum in treating the same.

ETIOPATHOGENESIS:

A. Dengue fever is a globally important arboviral infection transmitted by the Aedes genus of mosquito (primarily A aegypti, but also A albopictus), found in tropical and subtropical regions.

B. The infection is endemic in more than 100 countries, particularly the Southeast Asia region, western Pacific region, and the Americas

C. The mosquitoes were able to adapt to urban environments, where they lived in close proximity to people and bred in small water-containing collectors and vessels.

D. The virus outside the body has been found alive, if kept reasonably cool, in several instances up to 48 hours, and in one instance after 99 hours.3

E. Dengue fever is an acute, insect-borne fever of unknown etiology which is endemic in the Tropics and which at times becomes epidemic. It may spread to temperate regions in the hotter portions of the year.4

The etiologies for dengue virus infection are:

a) Viral replication, primarily in macrophages.5

b) Direct skin infection by the virus.

c) Immunological and chemical-mediated mechanism induced by host–viral interaction.6

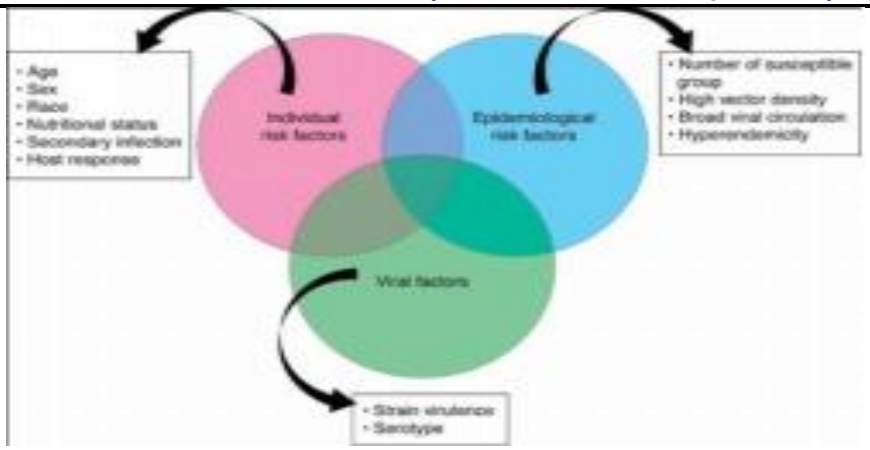

FIG. ETIOPATHOGENESIS OF DENGUE FEVER 7

CLASSIFICATION: They may range from subclinical infection to dengue fever, dengue hemorrhagic fever (DHF), and eventually dengue shock syndrome (DSS). As both cell tropism and tissue tropism of DENV are considered major determinants in the pathogenesis of dengue.

The WHO classifies Dengue fever into two groups:

A] Uncomplicated

B] Severe - Severe cases are linked to excessive hemorrhage, organ impairment, or severe plasma escape, and the remaining cases are considered uncomplicated.8

According to the 1997 classification, dengue can be divided into

1. Undifferentiated fever

2. Dengue fever

3. Dengue hemorrhagic fever.9

4. Dengue hemorrhagic fever was further subdivided into grades I–IV.

Grade I: Only mild bruising or a positive tourniquet test

Grade II: Spontaneous bleeding into the skin and elsewhere

Grade III: Clinical sign of shock

Grade IV: Severe shock - feeble pulse and blood pressure cannot be recorded.10 here, grades III and IV comprise Dengue shock syndrome.

CLINICAL MANIFESTATIONS &DIAGNOSIS:

A] Undifferentiated fever

This stage is seen mostly in the primary infection but may also occur following the initial secondary infection.

B] Dengue fever

Dengue fever follows both primary and secondary infections, and is most frequently encountered in adults and older children.

Onset of symptoms is characterized by:

A) Biphasic, high-grade fever lasting for 3 days to 1 week.

B) Severe headache (mainly retro bulbar), lassitude, myalgia and painful joint, metallic taste, appetite loss, diarrhea, vomiting, and stomach ache are the other reported manifestations.

C) Dengue is also known as breakbone fever because of the associated myalgia and pain in joints.

D) Of patients with Dengue fever, 50–82% report with a peculiar cutaneous rash.

E) The initial rash is the result of capillary dilatation, and presents as a transient facial flushing erythema, typically occurring before or during the first 1–2 days of fever. The second rash is seen at 3 days to 1 week following the fever, and presents as a asymptomatic maculopapular or morbilliform eruption.

F)Sometimes, individual lesions may merge and present as widespread confluent erythematous areas with pinpoint bleeding spots and rounded islands of sparing, giving a typical appearance of “white islands in a sea of red.”

G) The cutaneous rash is usually asymptomatic, and pruritis is reported only in 16-27% cases. Bleeding episodes are infrequently seen, although epistaxis and gingival

E] Dengue hemorrhagic fever- It is frequently seen during a secondary dengue infection. However, in infants it may also occur during a primary infection due to maternally attained dengue antibodies

F] Dengue shock syndrome

It is defined as dengue hemorrhagicfever accompanied by an unstable pulse, narrow pulse pressure (<20 mmHg), restlessness, cold, clammy skin, and cyanosis.

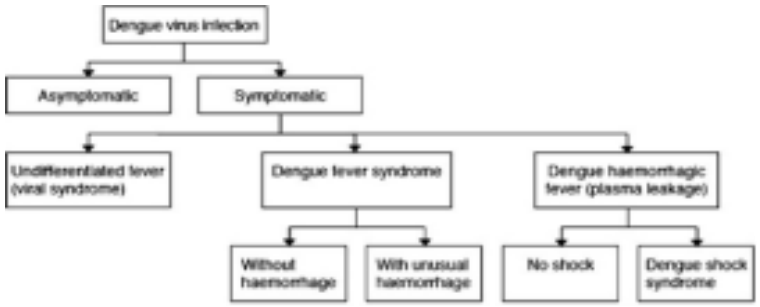

FIG. Clinical presentation of dengue fever.11

MANAGEMENTS OF DENGUE FEVER –

- Treatment depends upon the clinical presentation of severity of dengue fever .Common standard prescriptive medications include IV. PEPAR, IV .LINID, TABLET TAMIFLU, TABLET AZEE, TABLET DINEX GOLD, INJ. CEFACTIVE, INJ.AZTREONAM & IVF etc. MPS 40 mg is used to treat dengue fever with reduced platelet count.

EUPATORIUM PERFOLIATUM

- Eupatorium perfoliatum possesses anti-inflammatory, anti-oxidative, anti-plasmodial, anti-bacterial and antiviral activities.
- Eupatorium Perfoliatum extract and its few bioactive components i.e., quercetin, caffeic acid and eupafolin against wild primary clinical isolate of DENV-2 infection in an in vitro model.
- This remedy conforms to a low state of the body coming on, not with great rapidity, but rather slowly, such as you will find in marshy localities. It conforms to the marsh miasm, producing forms of chills and fever.
- It produces a very severe form of ague, and you will need to be conversant with this remedy, because when it appears no other remedy will cure your case.
- One of the grandest features running through this remedy is aching in the bones as if they would break, and hence it conforms to what the people commonly called the “break-bone” fever; and the common people have used it since early times for “break-bone” fever, and they have hence called it “bone set.”

- Acc to W. Boericke, it is known as "Bone-set", from the prompt manner in which it relieves pain in limbs and muscles that accompanies forms of febrile disease.
- Eupatorium acts principally upon the gastro-hepatic organs and bronchial mucous membrane. It is a boon in miasmatic districts, along rivers, marshes, etc, and in all conditions where there is a great deal of bone-pain.
- Cachexia from old chronic, bilious intermittent, Worn-out constitutions from inebriety, Sluggishness of all organs and functions, Bone-pains, general and severe soreness, marked periodicity.
- Fever --Perspiration relieves all symptoms except headache. Chill between 7 and 9 am, preceded by thirst with great soreness and aching of bones. Nausea, vomiting of bile at close of chill or hot stage; throbbing headache. Knows chill is coming on because he cannot drink enough.

Posology

§ 280 Sixth Edition [Law of Minimum Dose]

- The dose of the medicine that continues serviceable without producing new troublesome symptoms is to be continued while gradually ascending, so long as the patient with general improvement begins to feel in a mild degree the return of one or several old original complaints. This indicates an approaching cure through a gradual ascending of the moderate doses modified each time by succussion (§ 247).
- It indicates that the vital principal no longer needs to be affected by the similar medicinal disease in order to lose the sensation of the natural disease (§ 148).
- It indicates that the life principle now free from the natural disease begins to suffer only something of the medicinal disease hitherto known as homoeopathic aggravation.
- It is that amount of medicine, which is though smallest in quantity produces the least possible excitation of the vital force, and yet sufficient to effect the necessary changes in it (§ 246).
- Thus, we can conclude that the most appropriate dose would the one in the smallest quantity which is possible to produce the required changes.
- Choosing the potency for minimum dose depends upon -
    1. The susceptibility of the patient.
    2. The seat of the disease.
    3. The nature and intensity of the disease.
    4. The stage and duration of the disease.
    5. The previous treatment of the disease

Method of Measurement:

Assessment of Dengue Fever and its severity is done with the help of Dengue Severity Scale.

Dengue severity was classified into 4 grades, 27 based on bleeding episodes and shock, as Follows:

I. Grade 1: no evidence of bleeding, Positive Tourniquet test,
II. Grade 2: evidences of bleeding episodes,
III. Grade 3: presence of week and rapid pulse rate, low blood pressure, Or narrow pulse pressure,
IV. Grade 4: non measurable blood pressure or nonpalpable pulse
V. Grades 1-2 were classified as Dengue hemorrhagic fever and grades 3-4 were classified as Dengue shock syndrome 28

Improvement: "65% of the cases improved, i.e., 19 cases out of 30."

No improvement: "35% of the cases improved, i.e., 11 cases out of 30."

Outcome Assessment Criteria:

Dengue Fever typically is a self-limited disease with a mortality rate of less than 1% when detected early and with access to proper medical care.

ASSEMENT CRITERIA:

1) Absence of fever
2) Improved appetite
3) Normal vital signs
4) Normal platelet count
5) Urine output
6) Normal work of breathing
7) No evidence of bleeding
8) Stable hematocrit

METHODOLOGY:

1. Study Design: A three armed clinical trial is a clinical research experiment in which a new proposed treatment is compared against existing standard form of treatment. It consists of

I. 'Control group' which continues with the homoeopathy treatment.
II. 'Experimental group' which receives allopathic treatment with homeopathic medicines.

III. An 'Observational group' which is given the allopathic treatment.

- In this study we shall be comparing the effects of homoeopathic medicine. Eupatorium perfoliatum in dengue fever of adult population with a Experimental group of individual taking antiviral medications and other allopathic drugs according to symptomatology –TAMIFLU, AZTREONAM AND CEFACTIVE for viral fever .

2. Study Setting: Institutional OPD & IPD

3. Study Population: 1) Cases of dengue 2) Adult population

4. Sample Size: 30 cases

5. Sampling Technique: Purposive randomized samples.

6. Study Instruments/Data Collection Tools: Lab reports and hematological investigations.

7.. Method of Data Collection: Case record format ,Cases of Allopathic Hospital, World Health Organization , Previous Proposed Theories, Journals & Articles, medical records And Published Research Papers, Government Reports, classical textbooks, reference books and website.

8. Data Management and Analysis Procedure: Data would be compiled in Microsoft word and appropriate statistical tests would be applied at the end of the study.

9. Method of Selection of Study Subjects:

A. Inclusion Criteria:

1) Cases with dengue fever in the study were confirmed by laboratory tests.

2) Complaints of vomiting/nausea, abdominal pain, skin rashes, bleeding, headache, lethargy, retro orbital pain, diarrhea, hepatomegaly, etc.

3) Tourniquet test

4) Thrombocytopenia

B. Exclusion Criteria:

1. Age less than 15 years or more than 60 years.

2. Preexisting substantial chronic liver, kidney or heart disease.

3. History of Immune thrombocytopenic purpura.

4. Diagnosis of Malaria, Enteric fever.

5. Carcinoma

6. Immunocompromised patients.

7. Patients with psychiatric illness

8. Females with metrorrhagia

C. Withdrawal Criteria:

1. Lost to follow ups
2. Not Consensual
3. DAMA (discharge against medical advice)
4. LAMA (leave against medical advice)

RESULTS:

AGE GROUP		
15-30 years	Male	3
	Female	4
30-80 years	Male	16
	Female	7

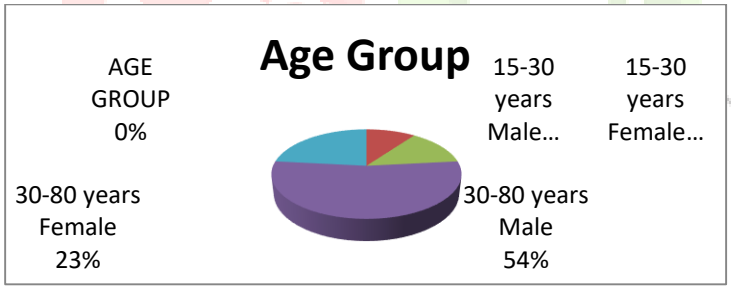

FIG. 1 -AGE GROUPS

GENDER DISTRIBUTION	
Male	19
Female	11

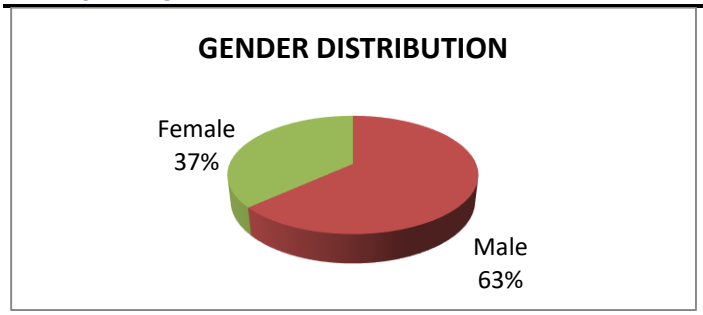

FIG.2 GENDER DISTRIBUTION

MARITAL STATUS		
MARRIED	MALE	13
	FEMALE	8
UNMARRIED	MALE	6
	FEMALE	3

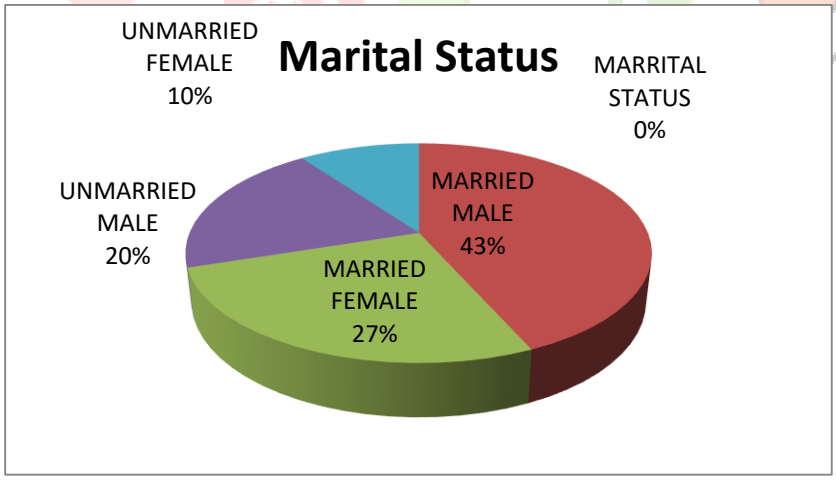

FIG.2- MARITAL STATUS

FEARFUL STATE OF MIND		
FEAR PRESENT	Male	6
	Female	7
ANATOMY PRESENT	Male	13
	female	4

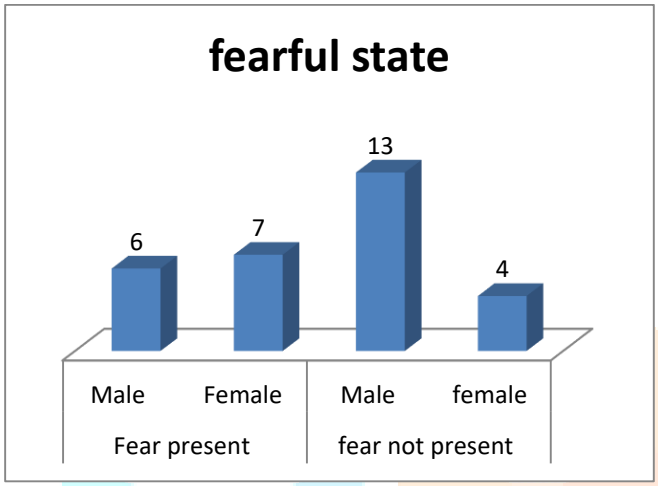

FIG3.FEARFUL STATE OF MIND

RESULT	FREQUENCY
IMPROVED	8
NOT IMPROVED	2

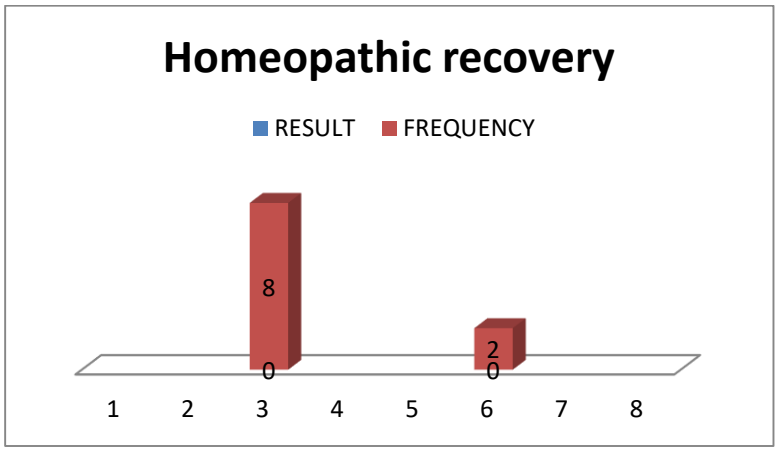

FIG 4-A]. HOMEOPATHIC RESULT WITH THE HELP OF EUPATATORIM PERFOLIATUM

RESULT	FREQUENCY
IMPROVED	6
NOT IMPROVED	4

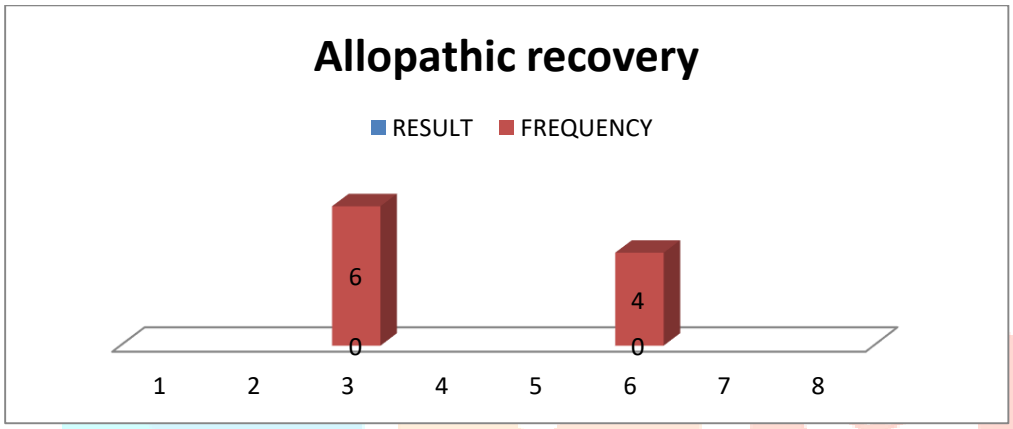

FIG 4-B]. ALLOPATHIC RESULT WITHOUT INTERVENTION OF HOMEOPATHIC MEDICINES

RESULT	FREQUENCY
IMPROVED	5
NOT IMPROVED	5

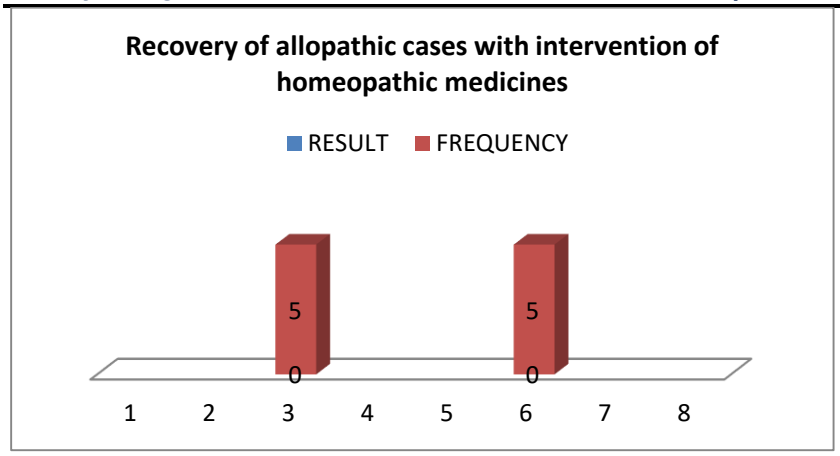

FIG 4-C]. ALLOPATHIC CASES IN WHICH EUPATORIUM-PERFOLIATUM GAVE FOR SPEEDY RECOVERY

Results:

Improvement: - "65% of the cases improved, i.e., 19 cases out of 30."

No improvement: - "35% of the cases improved, i.e., 11 cases out of 30.

STATISTICAL TESTS:

PRE-RX	POST-RX	MEAN
1	0	0.5
1	0	0.5
1	0	0.5
1	0	0.5
1	0	0.5
2	0	1
1	0	0.5
1	0	0.5
1	2	1.5
1	2	1.5
2	1	1.5
1	0	0.5
1	2	1.5
1	1	1
1	2	1.5
1	0	0.5
1	0	0.5
1	2	1.5

x diff= 0.133
standard deviation= 1
t test= 0.133/1/√30
t test= 0.133/1/5.48
t test= 0.133/0.182
t test= 7.307
p value= 1.895

1	3	2
1	1	1
1	0	0.5
1	3	2
1	0	0.5
1	0	0.5
1	2	1.5
1	0	0.5
1	2	1.5
1	0	0.5
1	2	1.5
1	3	2
MEAN =1.066667	MEAN= 0.933333	MEAN= 1

Before treatment mean: 1.066667

After treatment mean: 0.933333

T test

$$\boldsymbol{x\,diff} = Before\ treatment - after\ treatment$$

= 0.133

Standard deviation= 1

$\sqrt{n}$= 30

After substituting these values into the formula for *t* we have:

$$t = \frac{x\ diff}{\frac{standard\ deviation}{\sqrt{n}}}$$

$$t = \frac{0.133}{\frac{1}{\sqrt{30}}}$$

$$t = \frac{0.133}{\frac{1}{5.48}}$$

$$t = \frac{0.133}{0.182}$$

***t*= 7.307**

Determine critical value for *t* with degrees of freedom = 7.3 and α = 0.05.

In this critical value is 1.895

The calculated *t* exceeds the critical value (7.307> 1.895), so the means are significantly different.

DISCUSSION:

Dengue fever is an emergency situation which can lead to fatal results. Controlling dengue fever in appropriate time is need of the case. Eupatorium perfoliatum is known to have anti-pyretic properties. Its properties must be explored for benefit of mankind. 30 cases were collected from the college and the peripheral OPD. Cases with fever, fever with thrombocytopaenia, dengue haemorrhagic fever was prescribed in required potency.

According to the severity and frequency of fever the dose, repetition and change of medicine was selected. It was seen more number of males suffered from hemorrhage as compared to female in the study that is 65% male and 35% female patients were observed. About 12 cases were of dengue fever with thrombocytopenia, 3 cases of dengue hemorrhagic fever and 15 uncomplicated cases of dengue fever.

Out of 30 cases 19 cases that is 65% showed improvement and 11 cases that is 35% had no improvement. Keeping in mind the severity of fever cases with no improvement was either prescribed standard allopathic management. This study shows that eupatorium perfoliatum has potential role in controlling dengue fever. Yet further study with large sample size is needed to explore more anti-pyretic properties of Eupatorium perfoliatum.

CONCLUSION:

Out of 30 cases, 19 (65%) showed improvement, while 11 (35%) had no improvement. The cases with no improvement were either prescribed standard allopathic management.

This study suggests that Eupatorium perfoliatum may have a potential role in controlling dengue fever.

However, further research with a larger sample size is needed to explore its anti-pyretic properties more comprehensively.

Based on the severity and frequency of fever, the dose, repetition, and choice of medication were determined.

It was observed that a higher number of males suffered from hemorrhage compared to females, with 65% of male patients and 35% of female patients affected. Of the cases, 12 were diagnosed with dengue fever with thrombocytopenia, 3 with dengue hemorrhagic fever, and 15 were uncomplicated cases of dengue fever.

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