IJPSR (2015), Vol. 6, Issue 4 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 20 August, 2014; received in revised form, 27 October, 2014; accepted, 20 March, 2015; published 01 April, 2015

PROTECTIVE EFFECT OF POLYHERBAL SIDDHA FORMULATION-NILAVEMBU KUDINEER AGAINST COMMON VIRAL FEVERS INCLUDING DENGUE - A CASE-CONTROL APPROACH

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Keywords:

Siddha formulation,
Nilavembu Kudineer,
Protection effect, Viral fever

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ABSTRACT: Nilavembu Kudineer, a Siddha Polyherbal formulation, is a decoction concentrate widely used in Siddha Medicine to combat major type(s) of fevers including viral origin such as Dengue. **Methodology:** Study type: Prospective case-control with Retrospective data collection. Study Setting: National Institute of Siddha – it is a central Government Siddha Hospital, located at Chennai, Tamil Nadu and considered as an apex Institute for Siddha Medicine in India. Study Subjects: Patients reported at OPD. **Inclusion Criteria:** Fever patients with clinical symptoms of viral fever and / or Thrombocytopenia as "Cases". Patients without symptoms of viral fever but age-sex matched with case-subject as "Controls". A person who has consumed minimum 5 days of Nilavembu Kudineer was considered as Nilavembu consumed person. **Exclusion Criteria:** Malarial fever, Enteric fever, Filarial fever, Sepsis, Leptospirosis etc. Sample size: 176 cases and 352 controls. Study period: 4 months. Statistical tools: Odds Ratio, Conditional Logistic regression. **Results:** The odds of Nilavembu Kudineer consumed persons for developing viral related fever was 0.24 (CI: 0.13 to 0.45) which was statistically significant ($p < 0.0001$). Sex wise analysis reveals the odds of Nilavembu Kudineer consumed female persons for developing viral related fever was 0.47 (CI: 0.22 to 0.99) which was moderately significant ($p=0.048$). Whereas amongst the male group the odds was only 0.09 (CI:0.02 to 0.29) which was statistically highly significant ($p < 0.0001$). **Conclusion:** Consumption of Nilavembu Kudineer as a prophylactic measure prevents significantly the occurrence of Viral fever in all age groups invariably. The reason for low protection in female group could be due to different metabolic / or hormonal conditions during phases of age groups.

INTRODUCTION: Common cold, Influenza and Dengue have emerged as large public health problems over the last 50 years. The common cold is the most common human disease, which is caused by Rhino virus [1], Flu fever by seasonal and pandemic Influenza and Para influenza viruses and Dengue by four serotypes of Dengue virus.

QUICK RESPONSE CODE

DOI:
10.13040/IJPSR.0975-8232.6(4).1656-60

Article can be accessed online on:
www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(4).1656-60

Adults typically could contract two to five cold infections annually and children may have six to ten colds a year due to Rhino and Influenza viruses. This leads to huge work absences and taking a heavy toll on the economy. Rates of symptomatic infections increase in the elderly due to a worsening immune system. And there are more than 300 million people affected by Dengue around the world and at least one third of them are from India [2].

There has been a Dengue outbreak in Tamil Nadu during the later period of the year 2012. When the State was plagued by Dengue, Government of

Tamil Nadu has come out with public health advertisement promoting Nilavembu Kudineer as preventive and controlling the morbidity level of public on contracting viral fever. Further, government has made arrangements for the supply of decoction to all patients reporting for this purpose in Primary Health Centers and Government Hospitals.

Nilavembu Kudineer, a polyherbal formulation is a decoction concentrate widely used in Siddha Medicine to combat majority of fevers. Siddha is an ancient system of medicine founded by the sagely mystics with super intellect, who used their uncanny abilities for the betterment of mankind. It is largely practiced in Tamil speaking South Indian peninsula. For centuries, the traditional physicians practicing Siddha system of medicine have advocated the prevention and treatment of 'Pitha Suram' and 'Kaba Suram' (types of fever classification in Siddha system) using Siddha Medicine as it is mentioned in the Siddha literature [3].

The literature defines the 'Pitha Suram' to manifest the symptoms of hemorrhagic fevers; while the 'Kaba Suram' to have the symptoms of fever with upper and lower respiratory catarrh. The chief ingredient in the decoction is 'Nilavembu' (*Andrographis paniculata*) as it is called in Tamil. This herb popularly called the Neem of ground, Bile of earth and King of bitters is native to India and Sri Lanka. Anti-viral properties of Nilavembu have been investigated and established through pilot clinical studies, which showed promising results against common cold [4]; and *in-vitro* studies proved its efficacy against Dengue virus and Malarial parasite besides having anti inflammatory and immuno-modulatory properties [5]. The WHO technical work group has stated that currently there is no clear articulated theory to help and guide the kind of process in control of Dengue [6].

In this scenario, National Institute of Siddha, Chennai has made an attempt for evaluating the protective effect of Siddha Medicine against common viral fevers including Dengue through a case-control study when the state was plagued by Dengue and seasonal fevers.

MATERIALS AND METHODS:

The study was conducted in National Institute of Siddha, Chennai, Tamil Nadu State, India where an average of 2100 patients per day are visiting for Siddha system of treatment in Out-Patient-Department (OPD) of Ayothidoss Pandithar Hospital. The National Institute of Siddha has been functioning as an apex Institute for Siddha Medicine since October 2004 under the Department of AYUSH, Ministry of Health and Family Welfare, Government of India. There are six (6) consultation rooms and the Post-Graduate (P.G.) specialty Departments attend to the patients with assistance of faculty members and P.G. students. The OPD functions on all the 365 days of the year with the consultation hours from 8.00 AM to 12.00 Noon. All health care services are rendered free of charge. Patients irrespective of caste, creed or religion visit and avail the Siddha treatment.

The Hospital is equipped with Biochemistry, Clinical Pathology, Microbiology Laboratory divisions and provides diagnostic services for treatment. The King Institute of Preventive Medicine and Research (KIPMR), Chennai, Tamil Nadu, India has extended specialized laboratory services for screening the blood sample of Dengue suspected cases.

The study was conducted during the month of January and February, 2013. A specialized consultation room was opened for referring the patients with fever and constitutional symptoms. A case-record-form for collecting the data was designed and field tested for easy interaction with study subjects and recording data. Based on the clinical findings, the faculty members initially screened the fever patients for Dengue, Malaria, Enteric fever, Leptospirosis and/or other bacterial infections. Using exclusion and inclusion criteria eligible viral fever patients and Dengue seropositives were included as case group study subjects.

The control-group subject who was age and sex matched with a particular case-subject was drawn from other consultation rooms on the same day or within three (3) to four(4) days, and ensuring not suffering from viral fever for the past one month. The control-group was also interviewed and data

were recorded in the proforma. Since this study involves only interviewing the patients regarding their consumption of Nilavembu Kudineer and their personal characteristics. The Director as a head of the Institution granted approval for conduct of the study considering the provision of IEC waive off for minimal data collection study. The case-subject or control-subject who have consumed minimum five (5) days of Nilavembu Kudineer was considered as Nilavembu consumed person. Amongst study subjects some of the patients were tested positive for Dengue fever and these patients managed with Siddha treatment and the results were also presented.

Statistical Analysis:

All the collected data were entered into the computer system using an in-house designed Data Entry Module in MS Access Software. The data were analysed with statistical tools using STATA Software. The data were descriptively analysed for examining any difference between case-group and control-group. Chi-Square test was employed to determine the significance for univariate analysis.

Then, conditional logistic regression analysis was employed to determine the odds ratio for Nilavembu Kudineer consumption status with disease condition (viral fever). The odds ratio measure was used to determine the odds of occurrence of viral related fever in Nilavembu Kudineer consumed group over not consumed group. If odds ratio was less than 1, it was interpreted as less likely to develop the fever related condition. Probability (*p*) value of 0.05 was considered for statistical significance.

RESULTS:

A total of 176 cases and 352 controls were included in the study. Out of 176 cases, 81 (44%) and 95 (56%) were females and males respectively, and amongst controls, 162(46%) and 190(54%) were females and males respectively. It reveals that there was no difference in percentage of gender among cases and controls. The age groups less than 20 years, 21-30, 31-40, 41-50, 51-60 and more than 60 years were formed for examining any difference between case and control groups. The data shows that there was not apparent percentage difference in the age group between case and control groups. The minimum and maximum ages were three (3) and 79 years respectively. The mean ± standard deviation of age in case and control groups were 35.6 ± 18.1 and 35.8 ± 18.5 respectively, which was not statistically significant (p=0.90). Similarly, the same was not different in male (34.1 ± 17.6, 34.3 ± 18.3) and female (37.4 ± 18.5, 37.5 ± 18.8) groups separately for case and control groups. Nilavembu Kudineer had been consumed by nine (9) % and 27% in case and control groups respectively **Table 1**.

TABLE 1: CHARACTERISTICS OF STUDY SUBJECTS IN CASE AND CONTROL GROUPS

	Case	Control
Sex		
Female	81 (46%)	162 (46%)
Male	95 (54%)	190 (54%)
Total	**176**	**352**
Age (in years)		
<=20	42 (24%	85 (24%)
21-30	37 (21%)	72 (20%)
31-40	28 (16%)	55 (16%)
41-50	28 (16%)	54 (15%)
51-60	27 (15%)	56 (16%)
>60	14 (8%)	30 (9%)
Nilavembu		
Taken	16 (9%)	95 (27%)
Not taken	160 (91%)	257 (73%)

The **Table 2** shows that a total of 111 (63%) patients amongst cases reported within four(4) days of occurrence of fever and 25% of patients reported within eight(8) days. It is noted that 10% of patients report fever after 12 days. There was not much difference amongst male and female cases in the reporting period of fever symptoms **Table 2**.

TABLE 2: FEVER DISTRIBUTION IN CASE GROUP

Fever days	Female	Male	Total
<=4 days	47 (58%)	64 (67%)	111 (63%)
>4 and <=8	26 (32%)	19 (20%)	45 (25%)
>8 and <=12	0 (0)	2 (2%)	2 (1%)
>12 days	8 (10%)	10 (11%)	18 (10%)
Total	81 (100%)	95(100%)	176 (100%)

The conditional logistic regression analysis reveals that the odds of developing viral related fever among Nilavembu Kudineer consumed group was 0.24 (CI:0.13 to 0.46) which was statistically significant (p<0.0001). In other words when 100 persons develop viral fever among Nilavembu not

consumed group, only 24 persons would report with viral fever among consumed group. Age group was not significantly associated with odds of disease development and the reduction of odds was only influenced by consumption of Nilavembu Kudineer. The analysis was performed for Female and Male groups separately and it was found that the odds in female group was 0.47 (CI: 0.22 to 0.99) that was statistically moderately significant. However the odds in male group was 0.09(CI: 0.03 to 0.30) which was statistically highly significant **Table 3**.

TABLE 3: CONDITIONAL LOGISTIC REGRESSION FOR MEASURING THE ODDS

Study factors	Odds Ratio	SE	Significance	95% CI for OR	
				Lower	Upper
Nilavembu Kudineer	0.24	0.07	0.001	0.13	0.44
Age group	1.30	0.50	0.497	0.61	2.75
Female group Nilavembu Kudineer	0.47	0.18	0.048	0.22	0.99
Male group Nilavembu Kudineer	0.09	0.05	0.0001	0.02	0.29

SE: Standard Error, CI: Confidence Interval, OR: Odds Ratio

There were 62 persons who had taken Nilavembu Kudineer for one to four days during the study. If these study subjects were taken as Nilavembu Kudineer consumed group, the odds of developing viral fever was 0.64 (CI: 0.42 to 0.95) which was moderately significant (*p<0.027*). This result reveals that consumption of Nilavembu Kudineer for at least five days was essential for getting prevention effect.

Effect of Siddha Treatment on Dengue Fever:

A total of ten patients were tested positive for Dengue fever among the case-subjects. They were administered a prescribed regimen of treatment with 10 gm of *Adhatoda vasaca* leaves Karkam (Ground leaves paste) two times a day with water 30 ml of Papaya leaves juice two times a day and Nilavembu Kudineer (Andrographis decoction) made from 20 gm of coarse powder two times a day for a period of 15 to 20 days. Of all the ten (10) fever cases that tested positive for NS1 antigen and/or Dengue IgM, six (6) patients had thrombocytopenia at baseline.

These six patients when administered the above regimen of treatment showed substantial increase in the number of platelets as measured by the three parts Hematology analyzer by Sysmex Corporation Japan, calibrated periodically and Quality control run every day. Complete blood cell counting was done every day for one week. The quickest response in terms of increase in the number of

platelets in each patient is noted. In the other four (4) Dengue positive patients, who did not have thrombocytopenia at baseline, dip in the number of platelets was not observed during the administration of above regimen. This study conforms to and also validates the Siddha literature which says that "Adhatoda" has the properties to alleviate the hematological condition called '**Ratha pitham**'. 'Ratha pitham' in Tamil language translates into the meaning that the blood is heated up and seethes out. This is described as purpura and hemorrhage as manifestations of thrombocytopenia in modern medical terminology **Table 4**.

TABLE 4: CONTROL OF THROMBOCYTOPENIA IN DENGUE PATIENTS WITH SIDDHA MEDICINE

S.No	Age	Sex	Positive	Platelet	Date	Platelet	Date
1.	47	F	NS1,IgM, IgG	37000	5.12.12	140000	10.12.12
2.	11	F	IgM,IgG	100000	19.12.12	300000	22.12.12
3.	51	F	NS1,IgM,IgG	78000	27.12.12	270000	09.01.13
4.	27	F	NS1,IgM,IgG	139000	28.11.12	160000	1.12.12
5	24	F	NS1,IgM	66000	12.1.13	130000	15.1.13
6	38	F	IgM	64000	17.1.13	140000	29.1.13

DISCUSSION: There were many in-vitro studies that proved the inhibitory effect of Nilavembu (Andrographis paniculata) and its ingredients against Dengue and other viral agents causing fevers. A pilot double blind trial revealed the protective effect of Andrographis paniculata against common colds [4]. Also a clinical management study has shown the effect of Nilavembu Kudineer and Adathodai Manapagu in treating Dengue [5].

The outbreak of Dengue is seasonal and sporadic in certain pockets of tropical areas which makes difficult to conduct cohort or cross sectional studies as it requires a large population and resources. A case-control approach during the outbreak of Dengue is therefore a better scientific approach for evaluating the prophylactic efficacy of Siddha Medicine in preventing the occurrence of Viral fever and Dengue.

This study results corroborates the observations of earlier in-vitro and few clinical studies on the effect of Nilavembu Kudineer in preventing the multiplication of virus in humans [4, 5, 7]. While collecting data on consumption of Nilavembu Kudineer, number of days consumed during the 30 days interval, there were some study subjects who had taken the drug between one(1) and four(4) days. The analysis including all these subjects as Nilavembu taken group shows reduced preventive effect of the drug. When more than five (5) days taken group is considered, the effect of Nilavembu has increased significantly against the development of viral fever related conditions. These results emphasize that the consumption of Nilavembu Kudineer is providing protective effect only when taken adequately and regularly.

Also, when the Dengue subset is observed, it is inferred that the paste of Adathoda leaves and juice of Papaya leaves exert the quickest response in the bone marrow to produce platelets which would be life saving. The Nilavembu Kudineer which is reported to have anti Dengue viral properties by in-vitro cell line assays may play a role in the prevention of Dengue incidence which has to be confirmed by larger case control studies.

CONCLUSION: The anti-viral properties of Nilavembu and its effect as prophylactic activity makes it to be used as a public health measure to combat the viral infections causing fever including Dengue. The reason for low protection in female could be due to different metabolic and hormonal conditions during phases of age groups. The overuse of antibiotics in people infected with viral fever could be curtailed by administering the Nilavembu Kudineer (at least twice weekly) as discreet prophylaxis throughout the outbreak season.

ACKNOWLEDGMENT: The authors are thankful to all Post Graduate students and laboratory technicians of National Institute of Siddha and King Institute of Preventive Medicine and Research for their for assistance in various phases of this work.

REFERENCES:

1. Ron Eccles. Understanding the symptoms of the common cold and influenza. Lancet Infect Dis 2005; 5(11): 718-25.
2. Samir Bhat Peter W.Gething, Oliver J.Brady, Jane P.Messina, Andrew W.Farlow, Catherine L.Moyes et al; The Global distribution and burden of viral fever, Nature 2013, 496; 504-07
3. Kuppusamy Mudaliyar K N, Siddha maruthuvam pothu, 7th edition, 2007, Directorate of Indian Medicine and Homeopathy, Chennai-106, page - 20
4. Caceres DD, Hancke JL, Burgos RA, Wikman GK., Prevention of common colds with *Andrographis paniculata* dried extract. A pilot double blind trial. Phytomedicine 1997 ;4(2):101-4
5. Leon IC Tang, Anna PK Ling, Rhun Y Koh, Soi M Chye and Kenny GL Voon. Screening of anti-dengue activity in methanolic extracts of medicinal plants. BMC Complement Altern Med 2012, 12:3
6. Report of a WHO technical working group meeting on dengue prevention and control – WHO Headquarters, Geneva, Switzerland 10-12 December 2012
7. Kalai arasi, R., Jeeva Gladys, R., Elangovan, S., Soundararjan, D. K., Mubarak, H. and Kanakarajan, A. A combination of Nilavembu Kudineer and Adathodai Manapagu in the management of Dengue fever. Int. J. Cur. Res. 2013; Vol.5, Issue,04, pp.978-81

How to cite this article:
Christian GJ, Subramanian M, Periyasami D, Manickavasakam K, Gunasekaran P, Sivasubramanian S and Nijavizhi M: Protective Effect of Polyherbal Siddha Formulation-Nilavembu Kudineer against Common Viral Fevers Including Dengue - A Case-Control Approach. Int J Pharm Sci Res 2015; 6(4): 1656-60.doi: 10.13040/IJPSR.0975-8232.6(4).1656-60.