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Treatment of Dengue Infection; A Clinical Trial Focusing on the Effect of Silymarin on Clinical Features

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Abstract

Background: Dengue annually affects almost 100 million people globally while 2.5 billion people are at risk of developing dengue fever. The treatment of the infection is decided on the basis of the clinical features and level of fluids in the body. Liver is the main organ susceptible in dengue infection. Silymarin is a flavonoid which is known to play an important role in normalization of enzyme alanine amino transferase as well as aspartate amino transferase levels in hepatic disorders.

Objective: To assess the improvement in clinical features in dengue patients having silymarin treatment as compared to the placebo, along with conservative therapy.

Methods: A randomized controlled trial was conducted Ziauddin hospital, Clifton, Karachi. 92 dengue patients, aged 18 to 70 years, were included in the study and were equally divided into two groups, A and B, which received silymarin and placebo respectively, along with the symptomatic dengue treatment. The clinical features assessed included nausea, vomiting, bodyache, headache, retro-orbital pain, rashes, petechial haemorrhoids, facial flushing, conjunctivitis and hepato splenomegaly. The data were analyzed using SPSS version 20.0. Chi-square test and independent samples t-test were used for inferential analysis whereas the significance level was set at 0.05.

Results: The study results revealed that none of the liver enzymes were found to significantly decrease after the use of Silymarin in the treatment group as compared to the placebo group ($p>0.05$ for all). Moreover, none of the clinical features studied were found to be significantly different in both study groups ($p>0.05$ for all).

Conclusion: The study results revealed that none of the clinical features studied significantly improved in the treatment group as compared to the placebo group after Silymarin treatment. Further evaluation of the potential benefits of Silymarin therapy in the treatment of dengue infection is recommended.

Key words: Treatment; Dengue Infection; Clinical Trial; Silymarin; Clinical Features

Introduction

Dengue fever (DF) is associated with mosquito induced viral infection. It accounts almost 100 million subjects around the globe annually as well as2.5 billion persons are on the chance to develop the disease of dengue fever(1). After the end of second world war dengue has become a main community issue around the Asian countries and have been the major concern of emerging rapidly along with hemorrhagic fever(2). Causating factors of dengue fever includes DEN 1, DEN 2, DEN 3, and DEN 4virus strains (3). Few researches revealed that most of the dengue fever is cause by DENV-2and DENV-3 virus and can increase the hospital admissions and induces virus severity (4,5). However DENV-2 and DENV-3 still have dominancy to develop dengue infection in epidemic areas of Pakistan. The occurrence of dengue antibodies in the serum of patients having dengue fever represents the higher prevalence of DF plus DSS along with dengue shock syndrome and can lead to more deaths around the Pakistan(6). Annual occurrence of almost 2000 mortalities along with 390 morbidities indicates that the major cause is dengue fever. Excessive infectious places for dengue fever can promote the

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infectious burden and can transfer the infection from adolescence to child. Virus might be living inside body or can replicate closely within human.(7).Dengue Fever is mostly noncompliant but its symptoms begins with flu like illness and may lead to life threatening problems including bleeding manifestations, sudden loss of conscious and can lead to loss of many lives.(8). Patients have complains of fever for one week and almost 50% cases suffers from dermatological manifestations. Within first two days patients feel warm and redness on face or neck with red spots under the skin .(9).Clinical symptoms in dengue fever includes headache, fever, skin rashes, decrease white blood cell count and arthralgia. Due to high severity of pain, sometimes called as break bone fever. Dermatological manifestations begin just after patient appears to be afebrile (10). Dengue fever and Dengue hemorrhagic fever are diagnosed on the basis of clinical and epidemiological parameters that may be sometimes misleading. For assessing the treatment plan it is necessary to detect IgM and IgG antibodies in the patient blood. The difference in primary and secondary dengue infections can be assessed by general kits like ELISA (11). IgM and IgG antibody is located by ELISA kits in blood. For rapid diagnosis of the dengue virus NS1 antigen is used to detect in the patient's blood (12).Dengue is prevented by mosquitoes control and by protecting the subjects from mosquito bite. (13). Viral prevention strategies include properly disposing of waste, up gradation of water storage system and proper usage of repellents (11). There is no recommended vaccine for the eradication of the virus. Nevertheless, a newly tetravalent vaccine is invented but still it is on clinical trials. It consist of live attenuated vaccine and kills the inactive form of virus and causes recombinant protein envelope(14).The treatment of the infection is decided on the basis of the clinical features and level of fluids in the body. In the subjects, who are sensitive to fluids, they are recommended for intravenous hydration which leads to maximum hemodynamic benefits. According to WHO, the usage of crystalloid solutions in dengue patients is highly recommended. (15).Silymarin is related to flavonoid group and derived from the Silybummarian plant, a herbal medicine which is widely used in multiple studies to see improvement in patients with liver diseases. Silybum is made up of almost50% silibinin,that is related with original counter part of silymarin (16). Silymarin, primarily behaves as an antioxidant, decreasing the inflammatory agents like reactive oxygen species and lipid per oxidation, increases endogenous concentration of antioxidant enzymes such as glutathione peroxides, glutathione reductase, superoxide dismutase along with catalase (17). It plays a major role in boosting up the immune system as well as reduces fibrosis by inhibiting the apoptosis activation which occurs in stellate cells of liver. It also inhibits the collagen accumulation in parenchymal cells of liver(18). Many researches revealed that silymarin plays a main part in normalization of enzyme alanine amino transferase (ALT)as well as aspartate amino transferase (AST) levels in hepatic disorder.(19).

As liver is a susceptible organ in dengue infection, the present study was therefore designed to assess the improvement in clinical features in dengue patients having silymarin treatment as compared to the placebo, along with conservative therapy.

Methodology

The Study was designed as randomized control trial in which random sampling was used .It was conducted at Zia-uddin hospital, Clifton Karachi and completed within one year of duration. The Institutional review board of Ziauddin hospital Karachi has provided the ethical approval for this study. Total 92 cases were documented in this study after taking their informed consent. Cases were divided into two groups. Group A consist of 46 subjects were taking silymarin treatment and group B consist of 46 cases which were on placebo. The dengue cases who were diagnosed clinically, having positive serological test and the age between 18 to 70 years were included in this study. The subjects which were already taking silymarin therapy, known case of hepatic disorder, and those who refused for inform consent were excluded from the study. The demographic data includes age and sex. Clinical features including nausea, vomiting, bodyache, headache, retro-orbital pain, rashes, petechial haemorrhoids, facial flushing, infected conjunctiva and hepato splenomegaly were recorded.

Data Analysis

The data was entered and evaluated by using SPSS version 20.0. Frequencies and percentages were reported for gender, body ache, head ache and nausea.. T-test was used to evaluate the difference in quantitative variables. Association between the two groups was assessed by using chi-squared test. The significant p-value was set at < 0.05.

Results

A total of 92 patients were selected in present study. 60 (65.2%) were male and 32 (34.7%) were females with male to female ratio 2:1 in both the groups. Mean standard deviation of the age were recorded in two respective group as 38.39±17.08, 36.32±13.93 with p value 0.527.Subjects which had fever in two different groups had mean standard deviation with p value were 3.30±1.28 and 3.84±1.46 (0.061). In this study we have investigated the base line investigation in patients with dengue fever such as complete blood count, urea, creatinine, electrolytes and liver functions tests in two groups. Present study notice mean standard deviations of different parameters such as hemoglobin level had mean standard deviation in two groups were 13.89±1.87 and 13.92±3.04 with insignificant p value 0.957, few had mean standard deviation of PCV in two respective groups were 42.10±5.13, 41.17±4.68 (0.364), some had mean standard deviation of TLC were 3.62±1.55, 3.78±1.68 (0.644). Present studies have also noticed mean standard deviation of LFTs in two groups. The patients with mean standard deviation of direct bilirubin in both groups were 0.20±0.12, 0.25±0.18 (0.172) and for indirect bilirubin were 0.251±0.14, 0.42±0.42 (0.011), mean standard deviation of ALT subjects were recorded as 132.76±178.03, 107.32±93.86 (0.394), for GGT as 87.86±59.55, 87.86±59.55 (0.931) and for ALP were 79.54±37.05, 66.65±28.42. Cases with dengue fever having different sort of clinical presentations out of which,70.8% subjects suffering from nausea plus vomiting complains. 97.8% had headache, 58.6% had retro orbital pain, 82.6% had skin

Table 1:

Variables	Group A Mean ±S.D	Group B Mean ± S.D	p-value
Age (years)	38.39±17.08	36.32±13.93	0.527
Duration of Fever (days)	3.30±1.28	3.84±1.46	0.061
Hemoglobin (gm %)	13.89±1.87	13.92±3.04	0.957
Pack Cell Volume (%)	42.10±5.13	41.17±4.68	0.364
Total Leucocytes Count (x103 cells /cumm)	3.62±1.55	3.78±1.68	0.644
Platelets (x106 cells /cumm)	79.00±44.04	84.60±45.50	0.55
Sodium (mEq/L)	134.89±3.42	137.13±3.35	0.002
Potassium (mEq/L)	3.68±0.38	3.70±0.44	0.763
Urea (mg/dl)	19.26±7.53	19.41±6.67	0.919
Creatinine(mg/dl)	0.87±0.23	0.87±0.22	0.925
Serum Billirubin Direct (mg/dl)	0.20±0.12	0.25±0.18	0.172
Serum Billirubin Indirect (mg/dl)	0.251±0.14	0.42±0.42	0.011
Alanine Transaminase (U/L)	132.76±178.03	107.32±93.86	0.394
Gamma GultamylTransferase (U/L)	87.86±59.55	89.39±103.85	0.931
Alkaline Phosphates (U/L)	79.54±37.05	66.65±28.42	0.064

Table 2:

Clinical Features N		Group A		Group B		P-value
		%	N	%		
Nausea and vomiting	Yes	37	80.40%	28	60.90%	0.247
	No	9	19.60%	18	39.10%	
Bodyache	Yes	46	100.00%	44	95.70%	0.45
	No	0	0.00%	2	4.30%	
Headache	Yes	38	82.60%	36	78.30%	0.397
	No	8	17.40%	10	21.70%	
Retro Orbital Pain	Yes	26	56.50%	28	60.90%	0.416
	No	20	43.50%	18	39.10%	
Rash	Yes	36	78.30%	40	87.00%	0.205
	No	10	21.70%	6	13.00%	
Petechiae	Yes	1	2.20%	2	4.30%	0.5
	No	45	97.80%	44	95.70%	
Facial Flushing	Yes	31	67.40%	36	78.30%	0.174
	No	15	32.60%	10	21.70%	
Infected Conjunctiva	Yes	22	47.80%	26	56.50%	0.266
	No	24	52.20%	20	43.50%	
Hepatomegaly	Yes	0	0.00%	1	2.20%	0.5
	No	46	100.00%	45	97.80%	
Splenomegaly	Yes	0	0.00%	0	0.00%	0.5
	No	46	100.00%	46	100.00%	

Table 3:

Clinical Features			Group A		Group B		P-value
			n	%	n	%	
Bodyache	1st Day	Yes	46	100.00%	45	97.80%	0.5
		No	0	0.00%	1	2.20%	
	5thDay	Yes	0	0.00%	0	0.00%	0.5
		No	46	100.00%	46	100.00%	
Headache	1st Day	Yes	39	84.80%	36	78.30%	0.296
		No	7	15.20%	10	21.70%	
	5thDay	Yes	0	0.00%	0	0.00%	>0.999
		No	46	100.00%	46	100.00%	
Anorexia	1st Day	Yes	43	93.50%	46	100.00%	0.121
		No	3	6.50%	0	0.00%	
	5thDay	Yes	0	0.00%	1	2.20%	0.5
		No	46	100.00%	45	97.80%	

rashes, 3.3% were found petechias on different areas of body, few had a history of facial flushing and infected conjunctiva with 72.8 % and 52.1% patients. On abdominal examination in cases of dengue fever only 1 % had hepatomegaly. In present study we have determine the association between the group A which were on silymarin treatment and the group B on placebo with the patients had complains of bodyache, (0.05), (0.50), headache (0.29), (>0.99) and anorexia (0.12), (0.50) on 1st day and 5th day of treatment although present study did not find any significant association between them.

Discussion

The present study was designed to assess the improvement in liver function tests and clinical features in dengue patients having silymarin treatment as compared to the placebo, along with conservative therapy.

The study results revealed a significant difference only in the mean serum levels of sodium and indirect bilirubin in both study groups ($p<0.05$ for both). Furthermore, none of the liver enzymes were found to significantly decrease after the use of Silymarin in the treatment group as compared to the placebo group($p>0.05$ for all).Moreover, none of the clinical features studied were found to be significantly different in both study groups ($p>0.05$ for all).

Literature regarding potential benefit of bio flavonoids in the treatment of liver diseases is equivocal. A systematic review in 2001 reported Silymarin to have metabolic and cell-regulating effects such as carrier-mediated regulation of cell membrane permeability, inhibition of the 5-lipoxygenase pathway, scavenging of reactive oxygen species of the R-OH type and action on DNA-expression. In spite of this, no unambiguous conclusion can be drawn regarding the value of silymarin in the treatment of liver diseases (20).

Same is true for the role of silymarin in the treatment of dengue infection about which the heterogeneity of data prevents any decisive conclusions. Powers CN &Seltzer WN in 2016 reported that polyphenolic compounds, flavonoids, Chalcones, and other phenolics were the most strongly docking ligands for dengue virus protein targets as assessed by a virtual screening analysis of phyto chemical structures (21). Likewise, in a computer aided analysis of phytochemicals as potential dengue virus inhibitors in Pakistan, Qadir I et al., in 2017reported that five out of nine phytochemicals tested in the analysis proved to be novel dengue virus inhibitors out of which three were from silybummarianum(22).

On the other hand, Zindi K et al., in 2001 reported that among the various bioflavonoids studied only quercetin showed significant anti dengue virus type 2 inhibitory activities with other bioflavonoids showing minimal to no inhibition of viral activity (23).

The study results did not show any significant improvement in any of the studied clinical features of dengue infection in the treatment group given silymarin. Unfortunately, to the best of author's knowledge, there is virtual silence in the literature about any potential benefits of silymarin, or any silybummarianum derived phytochemical for that matter, in the context of improvement in the clinical features of dengue infection. A meaningful comparison of the relevant study findings therefore could not be made as a thorough literature search did not reveal any pertinent published data.

Conclusion

The study results revealed that none of the clinical features studied significantly improved in the treatment group as compared to the placebo group after Silymarin treatment. Further evaluation of the potential benefits of Silymarin therapy in the treatment of dengue infection is recommended.

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