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An Open-Label Clinical Trial to Evaluate the Safety & Efficacy of Siddha Sastric Medicines – Fixed Regimen in COVID-19 Positive Asymptomatic, Mild or Moderate cases - A Pilot Study

Research Article

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Abstract

Background: Covid-19 is a global pandemic since 2019. SARS-CoV2 is a new virus that originated from China and is currently spread across 160 countries. Siddha medicine is one of the traditional Indian medicines, part of Ayush that tend to treat several acute and chronic diseases. Aim: The objective of this study is to observe the safety and efficacy of Siddha regimen with lab parameters like LFT, RFT, RT-PCR, LDH, FERRITIN levels, and prevention of disease complications in covid-19 positive patients on the 7th day of treatment. Experimental Procedure: A non-randomized open-label observational retrospective study was designed. Twenty patients of either sex, of age between 18 and 60 years, were selected with proper consent. The covid patients who were confirmed by positive RT-PCR test results with or without clinical features of covid-19 were selected. They were treated with Siddha Regimen for seven days. Results: Sixteen out of 20 cases turned RT-PCR negative on their 7th day of treatment. And the Ct value of RT-PCR was statistically significant. LDH and Ferritin levels were reduced after the treatment even though the before treatment values are in the normal range. The LDH level was statistically significant on the 7th day of treatment. No Remarkable changes in the safety laboratory parameters like SGOT, SGPT, Blood urea, Serum Creatinine. Conclusion: Significant changes in efficacy laboratory parameters and no changes in safety laboratory parameters have been reported in the Siddha fixed regimen for covid-positive patients. All the 20 study participants were recovered without emergency and hospitalization.

Key Words: Siddha medicine, Covid-19, Indian Traditional Medicine, Ayush System of Medicine, Anti-viral, SARS-CoV2.

Introduction

Coronavirus disease (SARS-CoV2) is a life-threatening, major infectious disease that causes a global pandemic. It can affect all age groups. Although lesser mortality when compared with the MERS virus, it is causing panic all over the world. Although most infections are self-limited, about 15% of infected adults develop severe pneumonia that requires treatment with supplemental oxygen, and an additional 5% progress to critical illness. In severe cases, COVID-19 can be complicated by acute respiratory distress syndrome (ARDS), sepsis and septic shock, multiorgan failure, including acute kidney injury and cardiac injury (1). No specific antiviral drug has been proven effective for the treatment of patients with severe coronavirus disease 2019 (2). No one can predict the complications and serious events of this disease due to unknown clear Pathophysiology and direct anti-viral therapy. Most commonly the mortality is very high in above 50 age groups with co-morbid conditions like Diabetes, Hypertension, Bronchial Asthma, Cancer, etc.

Siddha's system of medicine is well known ancient Indian medical system. It contributes the biggest role in the management of Covid-19 disease. The ancient Siddha system of medicine considers the body as a conglomeration of three doshas known as *Vatham* (*Wind*), *Pitham* (*Fire*), and *Kabam* (*Water*), corresponding to the three elements of the universe. Equilibrium between the three doshas is necessary to maintain perfect health. Any derangement in the synergic action of these doshas transforms the body as a fertile ground to pop-up any infection (3). Siddha

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medicine has already played a major role in controlling the mortality rate of chikungunya and dengue in Tamil Nadu by the administration of *Nilavembu Kudineer* during 2015 (4). Many Siddha medicines have also been used during various viral outbreaks in Tamilnadu, like *nilavembu kudineer, aadathodai kudineer*, and *Kaba sura kudineer*. The primary aim of this study is to assess the safety and effectiveness of Covid-19 positive patients for Siddha Sastric Medicines and secondary is the role of Siddha regimen in preventing the disease severity on covid patients.

Pathophysiology

The SARS-CoV-2 infection enters the host cells through the S spike protein by binding to ACE2 for internalization and aided by TMPRSS2 protease. The high infectivity of the virus is related to mutations in the receptor-binding domain and acquisition of a furan cleavage site in the S spike protein. The virus interaction with ACE2 may down-regulate the anti-inflammatory function and heightens angiotensin II effects in predisposed patients (5). The invasion of the virus to the lung cells, myocytes, and endothelial cells of the vascular system resulting in inflammatory changes including edema, degeneration, and necrotic changes. These changes are mainly related to proinflammatory cytokines including interleukin IL-6, IL-10 and tumor necrosis factor α, granulocyte colony-stimulating factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, and increased expression of programmed cell death 1, T-cell immunoglobulin, and mucin domain 3 (6).

Comparison of Kaba Suram and COVID-19 (7)

The symptoms of Covid-19 are analogs with the symptoms of *KAPASURAM* mentioned in Siddha textbooks. In Siddha medicine, 64 types of fever are explained. One among them is *Kaba suram*. The Siddha textbook *Agsathiyar Sura nool 300* and *Sura vagadam* both explained about the *Kaba Suram*. The symptoms include *suram* (fever), *thondai varatchi* (sore throat), *nadukkam* (rigor), *vudal sorvu* (malaise), *vudal vali* (myalgia), *thalaivali*(headache), *vayirukazhithal* (diarrhea), *erumal* (cough), *marbil kozhaikattal* (sputum production) *mochu Vida siramum* (dyspnea), *mookkuneer paithal* (running nose), etc.

Materials and Methods

Trial registration

This clinical trial is approved by CTRI with registration no: ***CTRI/2020/08/027397*** [Registered on 26/08/2020] after getting approval from IEC of GSMC, Chennai with IEC No: ***GSMC-CH-3401/ ME-2/050/2019.*** All patients were given written information about the potential risks and benefits of participation in the study. Written consent was mandatory from each patient before inclusion in the clinical study.

Study Site - TPEC Covid-19 Care Centre, Vellore, Tamilnadu, India.

Selection of Drugs

Siddha Medicines' fixed regimen includes five Siddha Sastric medicines. All the study participants have been prescribed these medicines for 7 days. *Kaba Sura Kudineer Chooranam* converted into Decoction and administered 60 ml two times daily before 30 min of meals. *Kaba sura Kudineer* was prepared by adding 5 grams of powder with 240 ml of water and boiled into 60 ml. *Adathodai manapagu* was given 10 ml twice daily with warm water after meals. *Amukkara Chooranam Mathirai,* 500 mg tablets were administered in the dosage of two tablets three times daily after meals. *Thalisathi vadagam Mathirai*, 500 mg Chewable tablets were given two tablets three times daily after meals. *Brammanandha bairavam Mathirai* 100 mg tablets one (or) two pills administered two times daily after meals with honey depending upon the physical condition. All the medicines were procured from a standard GMP-certified IMPCOPS Company, Chennai.

Inclusion Criteria

The study included patients 18 to 65 years of age with COVID -19 Positive RT-PCR confirmed. COVID – 19 Positives with or without clinical signs and symptoms such as Sneezing, Cough, Sore Throat, Throat Pain, Malaise, Tiredness, Fever, loss of smell, loss of taste, chills were also included.

Exclusion Criteria

COVID - 19 extreme signs such as Respiratory distress (Respiratory Rate >24/ minute) and reduced Oxygen saturation (Spo2) < 95% at rest were excluded from this study. Patients with uncontrolled Diabetes HbA1c > 9% or FBS >140 mg/dl and stage 3 Hypertension (BP > 160/100 mmHg) and immune-compromised conditions like HIV, Hepatitis, Tuberculosis, Cancer were also exempted. The research did not include pregnant and lactating mot hers.

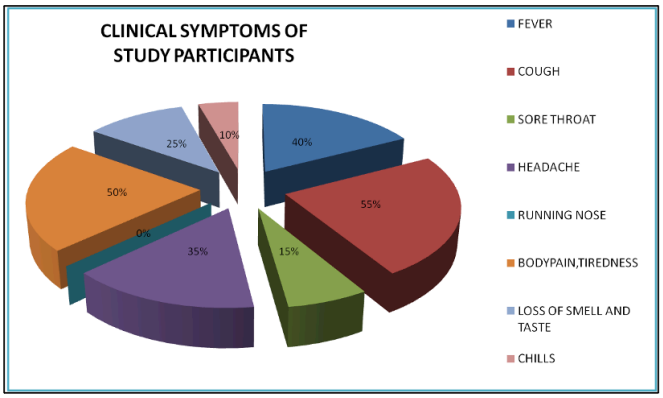
Selection of Cases and Observation of Data

From 47 positive cases, we obtained consent. 24 patients dropped according to the criteria on inclusion and exclusion out of 47 cases. In the remaining 23 cases, three have been reduced because of discontinuity. All other 20 cases were administered with Siddha-fixed regimen and the findings were evaluated by the protocol on the seventh day. Each case was documented with laboratory parameters.

Clinical Evaluation

Of the 20 subjects, 5 patients were asymptomatic during research inclusion. The remaining 13 patients showed distinct clinical symptoms and 2 were typical Influenza Like Illness (ILI). Seven cases were co-morbid in 20 cases. This study included 5 diabetic and 2 hypertensive cases.

Fig 1: Show Clinical Symptoms of Study Participants



Assessment of Haematological and Bio-chemical parameters and ADRs

The evaluation of the drug safety and efficacy was based on physical examination, vital signs, laboratory parameters like Complete Blood Count, LFT (Total, Direct, and Indirect Bilirubin, SGOT, SGPT, ALP enzyme levels), RFT (B.Urea and S.creatinine), CRP, LDH, FERRITIN, Prothrombin time and documentation of adverse effects. Participants were asked about any adverse effects daily during the rounds and the answers were recorded by the investigators. All patients were provided with the personal mobile number of the investigator for any emergency purposes. All the patients were frequently contacted through mobile phones during the study period for monitoring purposes. 7 ml of blood sample collected from all study participants on the 1st and 7th day of the intervention. The hematological and biochemical investigations of the clinical subjects before and after the clinical study were done in NABL accredited lab at GVMCH, Vellore.

Statistical Analysis

The results obtained were presented as mean+SEM. Safety and efficacy parameters were presented with a T-test to find the statistical significance. Values of $p<0.05$ were considered statistically significant, Values of $p>0.05$ were considered statistically not significant

Summary of Statistics

A paired T-Test was done on RT-PCR Results, Ct value before and after the Intervention to know the significance of Siddha intervention through statistical analysis. The negative test report is marked when RT-PCR Ct value reached 41. Most RT-PCR tests use Ct cutoffs of 35-40 cycles, so any sample with a Ct value below the cutoff, would be considered a true positive [19].The P-Value was significant (> .05) on RT-PCR, LDH, and platelet count results. It showed the efficacy of Siddha interventional medicines on covid-19 positive patients.

Table 1: Paired T-Test Results

Paired Samples Statistics					
Pair	**Mean**	**Std. Deviation**	**Std. Error Mean**	**t-value**	**P- Value**
B_urea_B	18.95	5.62	1.26	2.336	0.031
B_urea_A	16.35	3.72	0.83		
SGPT_B	27.05	13.08	2.93	-3.462	0.003
SGPT_A	51.55	34.43	7.7		
LDH_B	125.98	53.29	11.92	3.256	0.004
LDH_A	84.72	43.98	9.83		
Platelet_Count_B	273.35	61.46	13.74	-3.381	0.003
Platelet_Count_A	326.5	69.38	15.51		
RT_PCR_B	24.42	4.19	0.94	-11	<0.001**
RT_PCR_A	38.71	4.77	1.07		
SGOT_B	30.35	13.09	2.93	-1.847	0.08
SGOT_A	41.75	23.68	5.29		
Alk_Phosphatsase_B	80.45	15.98	3.57	-0.471	0.643
Alk_Phosphatsase_A	83.1	25.07	5.61		
Creat_B	0.85	0.14	0.03	0.754	0.46
Creat_A	0.83	0.2	0.05		
Ferritin_B	105.57	95.78	21.42	0.761	0.456
Ferritin_A	94.37	83.11	18.58		
Prothrombin_Time_B	13.69	1.26	0.29	1.04	0.312
Prothrombin_Time_A	13.37	1.54	0.35		

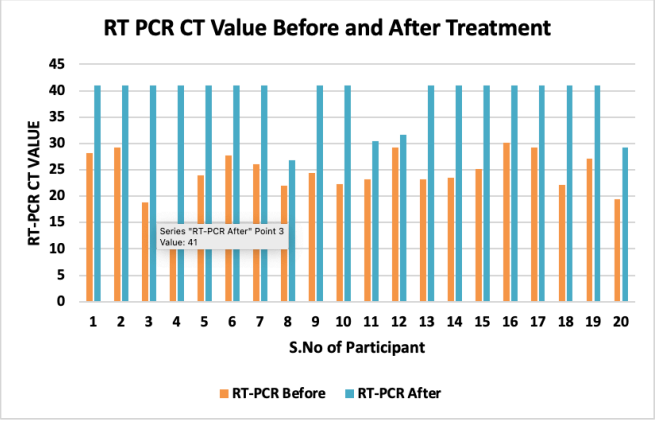
Table 1a: Significance and Non-Significance of the Results

S.NO	SIGNIFICANT	NOT SIGNIFICANT
1	B.Urea	SGOT
2	SGPT	ALP
3	LDH	S.CREATININE
4	PLATELET COUNT	FERRITIN
5	RT-PCR Ct value	PROTHROMBIN TIME

Results

Different clinical symptoms were reported in all of the 20 study patients under observation, with exception of 5 asymptomatic patients. It was observed that most of the clinical symptoms reduced on the fourth and fifth day of the intervention. 12 out of 15 symptomatic participants were entirely relieved from their symptoms like fever, cough, sore throat, fatigue, body pain, and chills on the 7 Th day of the intervention. The remaining 3 participants had mild symptoms like cough, fatigue after the intervention. There is a markable difference in the level of LDH, FERRITIN, and RT-PCR Ct value, Platelet count, Total Leukocyte count after treatment, on observation of the results (Table 1). And the safety lab parameters, like the B.Urea and S.creatinine, SGOT, SGPT, ALP enzyme levels, didn't significantly change. The level of urea in the blood before and after treatment is statistically meaningful (p-value < .05). The pre-and post-treatment level of SGPT is also statistically relevant (p-value <.05). The drug efficacy parameters LDH, Platelet count, and RT-PCR Ct value before and after treatment are also statistically significant (p-value < .05). The efficacy parameters LDH and Ferritin levels were reduced after the treatment even though the before treatment values are in the normal range. The levels of S. Creatinine, SGOT, ALP before and after treatment is (p-value > .05) statistically non-significant (Table 1 & 1a).

Fig 2: Shows RT_PCR CT Value Results before nad After Treatment



Discussion

The novel corona virus was identified as Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2) which causes Corona virus Disease 2019 (COVID-19) pandemic (8). There is currently no custom-made drug for the treatment of COVID-19. The discovery of the SARSCoV-2 vaccine is ongoing, and extensive attempts are being made to create a specific drug for that too. Yet, establishing the effectiveness and safety of some new agents could take some time. Drugs such as ribavirin and corticosteroids have significant side-effects (9). It was suggested that the lower mortality rate in mainland China and the relatively rapid response in controlling the SARS 2002 outbreak could have been due to the inclusion of herbal formulations from Traditional Chinese Medicine (TCM) in the treatment protocols (10).

Traditional Siddha medicine, which is mainly practiced in Tamil Nadu (southeastern India) is quite well among Tamil-speaking people around the world. Its literature is entirely in Tamil, one of the oldest Indian languages (11). In, Siddha system, herbs are used primarily along with animal and mineral substances. The name of 'Siddha' medicine was coined by sages called *Siddhars*, and those are the origin of medicinal practices. The objective of Siddha medicine is to make the positive health, and imperishable and harmonious blending of physical, mental, social and spiritual welfare of an individual to promote longevity. The Materia Medica of Siddha system includes drugs of plants, metals/minerals, marine products and animal products. This system is mainly based on the relationship between the universe and human body by interlinking five basic elements such as air, fire, water, earth and ether (12).

For Siddha practitioners, the interventional Siddha drug regimen is no new. These medicines have long been used in southern regions of India for various ailments. For this study, *Amukkara mathirai*, which includes *Amukkara or ashwagandha (Withania somnifera),* is a natural immune enhancer and adaptogenic herb that has greatly helped to covid patients in isolation ward from anxiety and stress. *Amukkara* is well known for its anti-inflammatory property. Recent work has demonstrated that COVID-19 infections have a large immune component and can result in the development of cytokine storm, a potentially life-threatening immune reaction in which the body releases too many cytokines into the blood at a rapid rate (13). It has demonstrated that Withaferine is capable of reducing the secretion of various proinflammatory cytokines (ex. TNFα, IL-6, IL-8, and IL-18) in a metastatic model of ovarian cancer (14). *Thalisathi vadagam mathirai* is a chewable tablet comprising dry ginger (*Zingiber officinale*), pepper (*Piper nigrum*), pepper root, *thalisapatri* (*Taxus buccata*), etc.

Kaba sura kudineer contains 15 herbs which include proven anti-pyretic, anti-viral, and immunomodulatory herbs including *Nilavembu (Andrographis paniculata), Seenthil (Tinospora cordifolia)*, and proven anti-tussive, expectorant, mucolytic herbs such as *adathodai (Justicia adathoda), thippili (Piper longum), karpooravalli (Plectranthus amboinicus)*, etc. Totally 37 compounds were screened from *Kaba Sura Kudineer,* of these 9 compounds showed high binding affinity against SARS-CoV-2 spike protein in silico docking study (15). In *Adathodai manapagu, the Siddha herb Adathodai (Justicia adathoda)* has a natural mucolytic, expectorant, bronchodilator property, and it is also useful in increasing platelet count. The medication *bramanandha bairavam mathirai* is a herbo-mineral formulation that in Covid patients has tended to control fever and rigor. *Brahmanandha bairavam mathirai* and *Vishnu chakram* have been used for the treatment of pyrexic phase of Chikungunya (16).

Of the twenty cases, except five, the remaining fifteen were observed with at least any of the above-mentioned clinical symptoms. The effectiveness of the Siddha intervention clinically indicated an improvement in the symptoms of Covid patients. The platelet count, the overall number of leukocytes, has been substantially increased and this can be due to the immunomodulatory effects of the Siddha regimen. This study involved covid-positive patients with a RT-PCR Ct value of 13-30. The RT-PCR Ct value reached 41 on the 7th day in 16 patients out of 20 study participants, after the intervention and was found to be Covid-19 negative. It tends to be the Siddha Regimen's anti-viral benefit. Although correlations were revealed, viral loads determined by real -time RT -PCR assays should not be yet used to indicate COVID -19 disease severity or to monitor therapeutic response. However, low Ct values indicating high viral loads may be used as an indication of transmissibility.

Elevated LDH levels seem to reflect that the multiple organ injury and failure may play a more prominent role in this pathology in influencing the clinical outcomes in patients with COVID-19 (17). Laboratory findings in patients with severe COVID-19 showed data consistent with cytokine storm involving elevated inflammatory markers, including ferritin, which has been associated with critical and life-threatening illness (18). The anti-inflammatory effect and effectiveness of the Siddha regimen in Covid-19 patients tends to be a substantial decrease in the levels of LDH and Ferritin after treatment.

When treated with the Siddha Regimen, several of the symptoms gradually subsided within seven days. No major changes were observed in the RFT, LFT marker levels that validated the safety of the Siddha regimen in covid-positive patients. Although the study was involved, only one study case was seen with hyperbilirubinemia. Upon observation, the total level of bilirubin was also lowered in that same case after the intervention.

No patients reported major adverse events and disease complications such as reduced oxygen saturation, cytokine storm, coagulopathy, viral-induced purpura, etc., on general study observation. It thus revealed the effectiveness of Siddha interventional drugs in Covid patients and helped to minimize patient hospitalization. Consequently, in *KABASURAM* and Covid -19, the Siddha regimen contains herbs and herbo-mineral regimens which are more beneficial. On improvement in clinical symptoms and with negative RT-PCR results, the study cases were discharged.

Concomitant Medications

Of the three out of 20, ORS powder was provided for their malaise and fatigue. Just one participant in the sample was administered with *Nilavembu kudineer* to manage fever. Nearly 6 study participants were treated with Siddha drugs *Elathy chooranam mathirai and Sangu parpam mathirai* for their gastric disturbances. Of the 20, only 2 were administered with the antihypertensive drug amlodipine 2.5 mg OD or BD during the study due to the rise in blood pressure. Just one study participant was handled with Siddha medication *Triphala chooranam* externally to wash his skin rashes. Steam inhalation has been prescribed for all patients with headache.

Conclusion

The case study of 20 positive patients with Covid shows that the formulation of Siddha Regimen has shown a strong response to the symptoms of Covid. On the 7th day of their treatment, 16 out of 20 turned negative. Out of 20, 15 were effectively treated for their symptoms. The effectiveness of the Siddha regimen on covid-positive patients was shown. No major adverse drug reaction (ADR) was triggered by the drug. In adolescents and geriatric age groups without any ADR, this combination is a safe and successful traditional symptomatic intervention to eliminate any covid complication. The administration of the preferred drug thus avoided hospitalization, thus minimising the expense of human productivity. To treat this devastating disease and manage the pandemic, India can use the abundance of comprehension existing in the Indian Systems of Medicine. This is also a valuable way to recognize the effectiveness of the Siddha system of medicine. But a limitation of this study is the 20 sample scale. In a wider population, this can also be accomplished.

Conflicts of interest

We announce that there is no conflict of interest in this study

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Declaration of competing interest

The authors do not report any conflicts of interest. The authors themselves are responsible for the outcome and drafting of the paper.

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