Journal of Ayurveda and Integrative Medicine 13 (2022) 100597

Contents lists available at ScienceDirect

Journal of Ayurveda and Integrative Medicine

journal homepage: http://elsevier.com/locate/jaim

Original Research Article

Safety and efficacy of siddha medicine preparation in the management of COVID-19: A prospective randomised open label study

K. Shanmugam [a], A. Nirmala [b], P. Parthiban [a], M. Pitchiah Kumar [a], C. Dhanam [a], S. Ganesh [a], K. Babu [a], T. Salaikarthikaiyan [a,*]

[a] Department of Indian Medicine & Homeopathy, Government of Tamil Nadu, India
[b] Govt.Medical College & ESI Hospital, Singanallur, Coimbatore, Tamilnadu, India

ARTICLE INFO

Article history:
Received 1 August 2021
Received in revised form
16 September 2021
Accepted 27 May 2022
Available online 3 June 2022

Keywords:
AYUSH
Traditional medicine
COVID-19
Clinical trial
CAM therapy

ABSTRACT

Background: The use of complementary and alternative medicine (CAM) therapies has surged since the spread of COVID-19 pandemic. However, the efficacy and safety of these CAM therapies remains majorly unexplored.
Objective: To understand the efficacy and safety of Nochi Kudineer Chooranam (5 gm), Mahasudarsan Chooranam (3 gm) , Adathodai Manapagu (10 ml), Omatheeneer (10 ml), Maldevi chenduram (100 mg) with honey in management of COVID 19 patients.
Methods: We conducted a randomised, controlled, open label trial in patients hospitalized with SARS-CoV-2 infection who had an oxygen saturation of 90% or more while breathing ambient air. Patients were randomized into two groups in a 1:1 ratio to either intervention group, receiving seven days of siddha medicine (Intervention group; n = 50) or standard care (control group; n = 50). The primary end point was clinical markers and patient recovery status on day 8.
Results: A total of 100 patients with confirmed COVID-19 with average age of 37 yrs (interquartile range, 28–49) participated in the study. There was no statistically difference between groups at baseline ($P > 0.05$). After intervention, patients in the intervention group had statistically ($P < 0.05$) significant reduction in the symptoms when compared to standard care. By end of the intervention period, 6 patients (12%) were hospitalized in the control group and none of them were reported for intervention group.
Conclusion: Among patients with mild to moderate COVID-19, 7 days of siddha medicine showed a significant reduction in the clinical symptoms and requirement of hospitalisation, with no adverse events. Therefore, the particular siddha medicine preparation could be used safely and effectively for the management of COVID-19 patients.
© 2022 The Authors. Published by Elsevier B.V. on behalf of Institute of Transdisciplinary Health Sciences and Technology and World Ayurveda Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Background

The severe acute respiratory syndrome coronavirus 2 (SARS – CoV-2) causes the new corona virus disease 2019 (COVID-19) pandemic. World health organization (WHO) had announced COVID-19 as a pandemic in March 2020 [1]. COVID-19 symptoms include cough, fever, acute respiratory distress syndrome (ARDS), severe dyspnea and pneumonia. Blood oxygen saturation (SpO_2) of ≤93% would require hospitalization and oxygen support. In 5% of all confirmed COVID-19 cases, critical care support may be required due to respiratory failure, septic shock, cardiac injury and/ or multiple organ failure [2]. Increasing number of trials are being widely carried out towards developing potential therapeutics and vaccines to combat the current pandemic [3].

Traditional and complementary medicines were observed to be particularly beneficial in the management of seasonal diseases. Siddha is one such traditional medicine practiced in south India for over 12,000 years [4]. COVID-19 is characterized by severe acute respiratory symptoms, including fever, cough, body pain and headache, with increased pro-inflammatory markers such as C-reactive protein (CRP) [5]. According to Siddha system of medicine, the pathophysiology and associated signs and symptoms of COVID-19 are classified under the disease category of *iya suram* [6].

* Corresponding author.
E-mail: salai.karthikaiyan@gmail.com
Peer review under responsibility of Transdisciplinary University, Bangalore.

https://doi.org/10.1016/j.jaim.2022.100597
0975-9476/© 2022 The Authors. Published by Elsevier B.V. on behalf of Institute of Transdisciplinary Health Sciences and Technology and World Ayurveda Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Therefore, the herbal preparations selected for the current study were related to *iya suram* in an attempt to combat the COVID-19 infection. The scientific documentation on the efficacy of siddha medicines in COVID-19 is inadequate [7–10]. The current study is aim to investigate the efficacy, safety, and scientific validity of traditional sastric siddha medication in the treatment of COVID-19.

2. Materials and methods

2.1. Study design

The current clinical study is a prospective randomized controlled trial (RCT) Ref: CTRI/2020/08/026999, carried out at Dedicated COVID care center (DCCC), Coimbatore, Tamil Nadu. The study population were patients hospitalized with COVID-19 infection (confirmed by RT-PCR of naso-pharyngeal swab), between October to December 2020. Clinical severity was fixed based on peripheral oxygen saturation >94% (mild), and between 90 and 94% (moderate). Written informed consent was obtained from all the patients and ethical approval obtained from the institutional review committee (IEC no: GSMS-CH-3401/ME-2/048/2019).

2.2. Sample size calculation

Sample size was calculated (n = 100) with the effect size = 0.6, alpha value = 0.05 and power = 0.80 using G*power 3.1.9.4 software. The actual sample size was 45 in each group, considering 5% attrition rate, a sample size of 50 in each group was finalized. A total of 100 asymptomatic or symptomatic patients with COVID-19 infection were enrolled for the study.

2.3. Inclusion and exclusion criteria

COVID-19 positive patients above the age of 18, confirmed with positive reverse-transcriptase polymerase chain reaction (rT-PCR) assay for SARS-CoV-2 virus were included. For inclusion, patients with mild clinical symptoms such as sneezing, cough, sore throat, throat pain, malaise, tiredness, fever, loss of smell, loss of taste were considered. Exclusion criteria included pregnancy and breast feeding females, COVID-19 positive patients with severe symptoms (oxygen saturation <90% at rest), metabolic disorders (diabetes, hypertension and morbid obesity) and having immune compromised status (HIV, hepatitis, tuberculosis, cancer).

2.4. Randomization

Using a computerised block randomization procedure (Random allocation software version 2), all patients were assigned to one of the two groups: intervention (n = 50) or control (n = 50).

2.5. Intervention details

Intervention group received *Nochi Kudineer Chooranam* (5 gm) in decoction form (50 ml) twice a day, *Mahasudarsan Chooranam* (3 gm) with warm water thrice a day, *Adathodai Manapagu (*10 ml) twice a day, *Omatheeneer (*10 ml) with water twice daily for 5 days, Maldevi chenduram (100mg) with honey twice daily for 5 days. Control group patients received standard conventional medication as per the recommendations of Indian council for medical research (ICMR).

2.6. Outcome measurements

COVID-19 symptoms were recorded and followed up every day for a period of seven days. Change in warning score (Temperature, Blood pressure, Heart rate, respiratory rate, oxygen saturation and level of consciousness) were recorded on case sheet record forms and then entered into an electronic format. Hematology markers (fasting blood sugar, haemoglobin, red blood cell count [RBC], white blood cell count [WBC Lymphocyte, Neutrophil, and Platelets], inflammatory markers (lactate dehydrogenase and C reactive protein), liver function markers (alkaline phosphatase, aspartate transaminase, alanine transaminase, serum bilirubin, albumin and globulin) and kidney function marker (creatinine) were estimated at baseline and at the end of 7 days for both the groups. The disappearance rate of the main symptoms (fever, shortness of breath, sore throat, body pain, cough, loss of smell, taste, and diarrhea) after the intervention period also carefully noted for both the groups.

2.7. Statistical analysis

The Kolmogrov–Smirnov test was used to determine whether the data was normal. A normal Gaussian distribution was shown by a p value greater than 0.05. As the data sets were normally distributed, paired and unpaired t test were done to compare the mean differences between intra and inter group using R statistical software version 4.0.2.

3. Results

Of the 280 users evaluated, 100 (35.7%) were enrolled and 180 (64.28%) did not comply with the eligibility criteria. The majority was male (60%), and the average age was 37 years (standard deviation, SD = 12). Fig. 1 depicts the study flow chart. In terms of age, sex, temperature, blood pressure, heart rate, respiratory rate, blood oxygen saturation, and other baseline data, there was no statistically significant difference between the two groups, and they were comparable (Table 1).

3.1. Outcome measures

Table 2 shows a comparison of clinical indicators in the control and intervention groups. Except for Hb, Neutrophil count, and Platelet count, no other clinical parameters were significantly different between the two groups at the end of the intervention. After one week of treatment, 92.5% of patients in the intervention group and 78.8% of patients in the control group had improved coughing symptoms, as presented in Table 3. The Chi squared test revealed that this difference was significant (p value = 0.03), indicating that the intervention group's rate of coughing improvement was higher. In addition, 82.3 percent of patients in the intervention groups and 50% of patients in the control groups experienced significant (p = 0.02) smell recovery. The intervention group had a relief rate of 78.9%, while the control group had a relief rate of 25% for body pain, which was statistically significant (p value = 0.03). As the results showed in the Table 4, hospitalization rate in the control groups was 12% and none of them were reported for intervention group and Fisher exact test supports a significant difference (p value = 0.04).

4. Discussion

A wide rampant increase in the spread of COVID-19 pandemic across the globe necessitates the need for an effective and safe management of the pandemic and its associated co-morbidities. The current study demonstrates the safety and efficacy of Siddha medicine in the management of COVID-19. This is one of the first ever documented evidence on the beneficial effects of siddha medicine for COVID-19 management. The primary beneficial effect

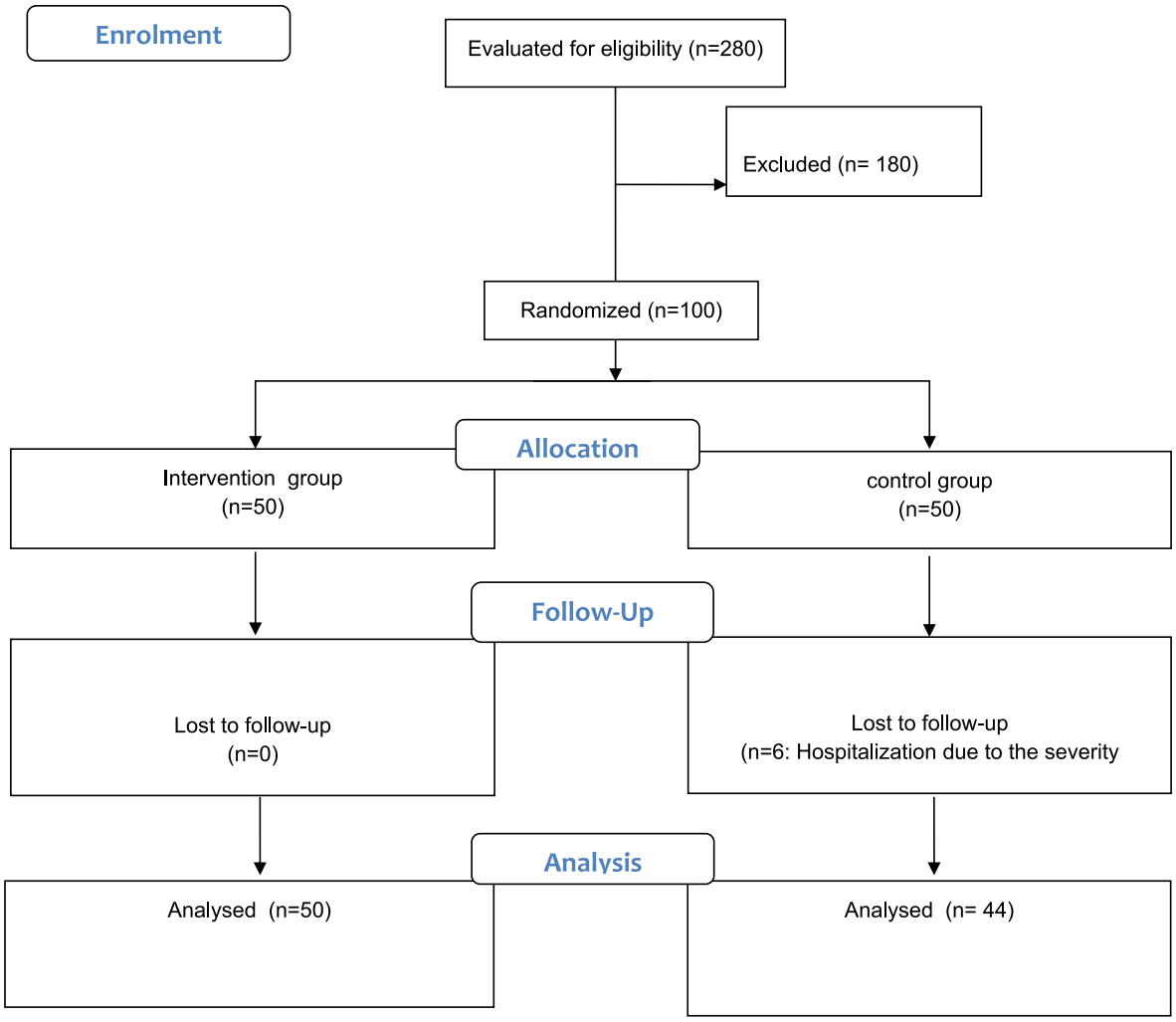

Fig. 1. CONSORT statement.

Table 1
Baseline Demographic and Clinical Characteristics of the participants.

Characteristic	Control Group	Experimental Group
Age (yrs)	34 (19–59)	37 (19–59)
Sex (M/F)	25/25	25/25
SBP (mmHg)	127 (83–156)	126 (90–182)
DBP (mmHg)	80 (59–98)	79 (56–129)
Pulse rate (bpm)	93.5 (58–133)	89.5 (66–130)
Body temperature (°C)	97.4 (96–98.9)	98.9 (96–99.1)
Respiratory Rate (bpm)	21 (17–23)	21 (19–24)
SaO_2	97 (90–99)	97 (92–99)
Diabetes (Yes/No)	9/41	8/42
Hypertension (Yes/No)	1/49	3/47
Asthma (Yes/No)	1/49	3/47
Obesity, BMI > 30 (Yes/No)	6/44	4/46
History of Fever (Yes/No)	4/46	16/32
Cough (Yes/No)	3/47	27/22
Sore throat (Yes/No)	6/44	15/34
Diarrhoea (Yes/No)	1/49	5/44
Loss of smell (Yes/No)	6/44	17/33
Loss of taste (Yes/No)	2/48	14/36
Body pain (Yes/No)	3/47	19/31
Shortness of breath (Yes/No)	0/49	8/42
Days from symptom onset to randomization (Mean ± SD)	4.75 ± 1.82	5.5 ± 2.76

observed in the study was improvement in the COVID-19 symptoms. The COVID-19 related symptoms like cough disappeared at the end of intervention period in 92.5% patients in the intervention group when compared to 75% in the control group. Loss of smell is one of the characteristic and classical symptoms of COVID-19, and the particular symptom disappeared in 82.3% patients in the intervention group when compared to 50% in control group. Reduction in body pain was another important symptom which showed significant reduction in the intervention group. Based on the eight points ordinal scale used in our study to assess the clinical outcomes in which the patients were placed in eight groups ranging from 1 (discharge with no limitation of activities) to 8 (death), we observed that out of 50 patients treated with siddha medications, all of them were discharged without no limitations in performing their everyday activities. Whereas out of 50 patients taking standard conventional medicines, 44 were discharged with no limitation to perform their everyday activities, while 6 patients (12%) required hospitalization. And 5 were hospitalized requiring no oxygen supply and 1 patient hospitalized with requirement for oxygen supply. Likewise, a significant improvement is observed in the clinical parameters such as neutrophil and platelet count, but no significant difference between groups in other clinical

Table 2
Clinical parameters between the control and intervention group.

Variables	Control Group		Experimental Group	
	Day 1	Day 7	Day 1	Day 7
Fasting Blood sugar (mg%)	123.39 ± 50.91	115.60 ± 41.17	115.72 ± 42.94	110.0 ± 24.35
Serum Creatinine (μmol/L)	0.81 ± 0.15	0.77 ± 0.14	0.80 ± 0.18	0.80 ± 0.15
Serum Bilirubin	0.72 ± 0.10	0.70 ± 0.10	0.71 ± 0.10	0.71 ± 0.13
SGOT	25.41 ± 6.88	21.99 ± 6.19	24.82 ± 8.93	25.48 ± 9.78
SGPT	29.56 ± 17.36	29.60 ± 15.69	28.80 ± 18.36	25.32 ± 25.32
ALP	152.53 ± 39.10	155.08 ± 39.05	143.62 ± 38.52	150.43 ± 40.50
Serum Albumin	4.34 ± 0.22	4.23 ± 0.26	4.25 ± 0.28	4.21 ± 0.28
Serum Globulin	2.93 ± 0.38	2.81 ± 0.52	2.85 ± 0.46	2.83 ± 0.44
LDH	494.18 ± 130.88	430.70 ± 130.82	476.40 ± 133.44	428.23 ± 120.64
C-Reactive Protein	16.09 ± 14.20	14.06 ± 14.50	20.10 ± 24.42	14.58 ± 11.85
WBC ($\times 10^9$/L)	5.81 ± 1.39	6.99 ± 1.86	6.27 ± 2.04	6.84 ± 1.98
RBC	4.96 ± 0.42	4.87 ± 0.45	4.81 ± 0.46	4.73 ± 0.41
Hb (g%)	13.75 ± 1.42	13.53 ± 1.54	13.13 ± 2.03	12.86 ± 1.87[b]
Lymphocyte count ($\times 10^9$/L)	2.24 ± 0.52	2.58 ± 0.68	2.22 ± 0.88	2.30 ± 0.56
Neutrophil count	48.27 ± 10.06	51.65 ± 9.94	52.87 ± 11.06	55.44 ± 8.69[b]
Platelet count	218.93 ± 95.06	270.95 ± 92.58[a]	223.37 ± 92.80	253.32 ± 73.09[a]

[a] Paired t test.
[b] Unpaired t test.

Table 3
Disappearance of COVID 19 related symptoms after the intervention.

Variable	Control Group	Intervention group	P value
Fever	4/4 (100)	16/16 (100)	-
Cough	2/3 (75)	25/27 (92.5)	**0.03**
Sore throat	3/6 (30)	12/15 (80)	**0.01**
Diarrhoea	1/1 (100)	5/5 (100)	-
Loss of smell	3/6 (50)	14/17 (82.3)	**0.02**
Loss of taste	2/2 (100)	13/14 (92.8)	**0.98**
Body pain	1/3 (25)	15/19 (78.9)	**0.03**
Shortness of breath	–	8/8 (100)	-

Table 4
Hospitalization rate in control and experimental group.

	Control group		Intervention group		P value
	Yes	No	Yes	No	
Hospitalization, n (%)	6 (12)	46 (92)	0	50 (100)	0.04

parameters. On a broader aspect, siddha medicine was found to be as effective as or even better in most aspects when compared with conventional medicine. We have used special combaination of the herbal formula for the Covid 19 infection, its very hard to compare the effects with other drugs in the similar conditions as well.

Another important finding of current study is regarding the safety of using a siddha medicinal preparation. A common misconception regarding siddha system of medicine is to consider all siddha medicines to have high level of toxicity on Liver and Kidney [11]. The liver function tests (SGOT, SGPT & ALP) and the serum creatinine levels were measured in the current study, and they were well within the range post-intervention, demonstrating the safety of siddha medicines in the management of COVID-19. LDH and CRP levels are reported to be useful and effective markers in the monitoring the prognosis and treatment responses in COVID-19 [12]. When compared to the control group, the intervention group had significantly lower levels of LDH and CRP.

4.1. Limitation

To our knowledge, this is one of the first study conducted on a specific siddha preparation to treat COVID-19 and measuring its safety and efficacy. The current study was carried out in patients affected during the first wave of COVID-19. The major limitation of the current study is the uncertainty on whether the noticed efficacy could be observed in the delta variant of COVID-19 or for possible further waves of COVID-19.

4.2. Future direction

The documented beneficial effects observed in the current study is very promising in the future management of COVID-19, especially the safety of the siddha preparation being clearly demonstrated in the study. Future adequately powered trials with larger sample size would be of greater help in substantiating our findings.

5. Conclusion

Our findings indicate that COVID-19 patients treated with siddha regimen shows significant improvement in clinical outcomes and reduction in requirement for hospitalization. This siddha regimen can be used effectively for the management of COVID-19.

Author contribution

K.Shanmugam, C.Dhanam, M.Pitchiah kumar, P.Parthipan, and S.Ganesh: Conceptualization, Methodology, K.Shanmugam, A.Nirmala, and K.Babu: Intervention and Data curation, K.Shanmugam and T.Salaikarthikaiyan: Writing- Original draft preparation, C.Dhanam, A.Nirmala and, K.Babu: Supervision, K.Shanmugam and T.Salaikarthikaiyan Writing- Reviewing and Editing.

Supplementary data link

Nil.

Funding source

No external funding was received for this study.

Declaration of competing interest

The authors declare no conflict of interest.

References

[1] World Health O. Responding to community spread of COVID-19: interim guidance, 7 March 2020. World Health Organization; 2020.

[2] Maheshkumar K, Wankhar W, Gurugubelli KR, Mahadevappa VH, Lepcha L, Kumar Choudhary A. Angiotensin-converting enzyme 2 (ACE2): COVID 19 gate way to multiple organ failure syndromes. Respir Physiol Neurobiol 2020: 103548.

[3] Rabaan AA, Al-Ahmed SH, Sah R, Tiwari R, Yatoo MI, Patel SK, et al. SARS-CoV-2/COVID-19 and advances in developing potential therapeutics and vaccines to counter this emerging pandemic. Ann Clin Microbiol Antimicrob 2020;19(1):1–37.

[4] Thileepan T, Prasad VM. Literature review of suram (fever) in siddha medicine. J Res Tradit Med 2018;4:21–5.

[5] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727–33.

[6] Rathinam S, Muthiah K, Parameswaran S, Tamilarasan K, Selvarajan E, Ayyasamy U. Analogy of Kaba Suram with COVID-19 symptoms-A siddha literature review. Int J Ayurvedic Med 2020;11(4):616–21.

[7] Srivastava A, Rengaraju M, Srivastava S, Narayan V, Gupta V, Upadhayay R. A double blinded placebo controlled comparative clinical trial to evaluate the effectiveness of Siddha medicines, Kaba Sura Kudineer (KSK) & Nilavembu Kudineer (NVK) along with standard Allopathy treatment in the management of symptomatic COVID 19 patients - a structured summary of a study protocol for a randomized controlled trial. Trials 2021;22(1):130.

[8] Chitra SM, Mallika P, Anbu N, NarayanaBabu R, SugunaBai A, David Paul Raj RS, et al. An open clinical evaluation of selected siddha regimen in expediting the management of Covid-19 –a randomized controlled study. J Ayurveda Integr Med 2021;13(1):100397.

[9] Srivastava A, Rengaraju M, Srivastava S, Narayan V, Gupta V, Upadhayay R. A double blinded placebo controlled comparative clinical trial to evaluate the effectiveness of Siddha medicines, Kaba Sura Kudineer (KSK) & Nilavembu Kudineer (NVK) along with standard Allopathy treatment in the management of symptomatic COVID 19 patients-a structured summary of a study protocol for a randomized controlled trial. Trials 2021;22(1):1–3.

[10] Meenakumari R, Thangaraj K, Sundaram A, Sundaram MM, Shanmugapriya P, Mariappan A, et al. Clinical outcomes among COVID-19 patients managed with modern and traditional Siddha medicine-a retrospective cohort study, Chennai, Tamil Nadu, India, 2020. J Ayurveda Integr Med 2021;13(2):100470.

[11] Priya R, Sujatha V. AYUSH for COVID-19: science or superstition? Indian J Publ Health 2020;64(6):105.

[12] Sharifpour M, Rangaraju S, Liu M, Alabyad D, Nahab FB, Creel-Bulos CM, et al. C-Reactive protein as a prognostic indicator in hospitalized patients with COVID-19. PLoS One 2020;15(11):e0242400.