Original Research Article

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

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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 (SpO2) 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 iyu suram [6].
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 siddha siddha 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 assessed using prograde oxygen saturation >94% (mild), and between 90 and 94% (moderate). Informed written 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. Hematological markers (fasting blood sugar, haemoglobin, red blood cell count (RBC), white blood cell count (WBC) and Neutrophil, and Platelet), 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 disappearance rate of the main symptoms (fever, shortness of breath, body pain, cough, loss of smell, taste, and diarrhea) after the intervention period also carefully noted for both the groups.

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
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 limitations in performing 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

| 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 (58–132) | 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)        |
| SaO2                           | 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 |
4.1. Limitation

levels of LDH and CRP.

Another important finding of 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.Parthiban, 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

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Declaration of competing interest

The authors declare no conflict of interest.
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