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Efficacy of individualized homeopathy as an adjunct to standard of care of COVID-19: A randomized, single-blind, placebo-controlled study

Debadatta Nayak [a,*], Juhi Gupta [b], Anupriya Chaudhary [c], Krishna Gopal Singh [d], Abhijeet Deshmukh [e], Deblina Das [a], Abhishek Saha [f], Deepak Kumar [a], Ashwini Kumar [a], Ajay Goenka [g], S.K. Mishra [h], Sanjay Gupta [i], Anil Khurana [j]

[a] Epidemic Cell, Central Council for Research in Homoeopathy, 61-65, Institutional Area, Janakpuri, New Delhi, 110058, India
[b] Dept. of Physiology, Government Homoeopathic Medical College and Hospital, AYUSH Campus, MACT Hills, Kaliasot Dam Approach Rd, Chuna Bhatti, Bhopal, Madhya Pradesh, 462003, India
[c] Dept. of Clinical Research, Central Council for Research in Homoeopathy, 61-65, Institutional Area, Janakpuri, New Delhi, 110058, India
[d] Dept. of Pulmonary Medicine, Chirayu Medical College & Hospital. Bhopal-Indore Highway Bhainsakhedi, Bairagarh, Bhopal, Madhya Pradesh, 462030, India
[e] Dept. of Surgery, Chirayu Medical College & Hospital, Bhopal-Indore Highway Bhainsakhedi, Bairagarh, Bhopal, Madhya Pradesh, 462030, India
[f] Intermediary Pharmacovigilance Centre (Homoeopathy), National Institute of Homoeopathy, GE Block, Sector-III, Salt Lake, Kolkata, 700106, India
[g] Chirayu Medical College & Hospital, Bhopal-Indore Highway Bhainsakhedi, Bairagarh, Bhopal, Madhya Pradesh, 462030, India
[h] Government Homoeopathic Medical College and Hospital, AYUSH Campus, MACT Hills, Kaliasot Dam Approach Rd, Chuna Bhatti, Bhopal, Madhya Pradesh, 462003, India
[i] Dept. of Practice of Medicine, Government Homoeopathic Medical College and Hospital, AYUSH Campus, MACT Hills, Kaliasot Dam Approach Rd, Chuna Bhatti, Bhopal, Madhya Pradesh, 462003, India
[j] Central Council for Research in Homoeopathy, 61-65, Institutional Area, Janakpuri, New Delhi, 110058, India

1. Introduction

The Coronavirus disease 2019 (COVID-19) pandemic due to SARS-CoV-2 spread rapidly, encountering a population that had no immunity and unprepared healthcare systems. The virus claimed many lives. So far, the pandemic has led to 93,805,612 cases and 2,026,093 deaths as of 19th Jan. 2021 [1]. COVID-19 has indeed perplexed the medical system with its pervasive symptomatology, multiorgan involvement, and a wide spectrum of disease severity ranging from asymptomatic to symptomatic mild, moderate, to severe requiring intensive care management, and to the disease being fatal [2]. As per World Health Organization (WHO), about 80% of infections are mild-to-moderate or asymptomatic; 15% develop severe disease and 5% have a critical disease with complications [3]. Presently, there is no anti-viral specific to COVID-19. Multiple different therapeutic options like antimalarial, HIV medications, antivirals, antihelminthics, and steroids have been repurposed for the management of COVID-19 in various phases of the pandemic and studies have been undertaken to estimate their efficacy [4]. Similarly, various homeopathic medicines were also suggested for prophylaxis and treatment of COVID-19, and research studies are in progress [5]. Recently, remdesivir has been widely recommended for COVID-19, including the United States Food and Drug Administration (US FDA), but further clinical trials have not been able to support significant clinical benefit. Currently, no other therapeutic agents have been proven to be effective in the treatment of patients with COVID-19 [6].

Homeopathy is one of the popular systems of complementary medicine and has been used in epidemic outbreaks in the past. Homeopathy has been used for treatment and prevention in the epidemics of Cholera, Spanish flu, Dengue, Chikungunya, Acute encephalitis syndrome, etc with variable success [7,8]. There is anecdotal evidence that homeopathy was successful during the Spanish flu epidemic of 1918, in which at least 20–50 million people died worldwide [9]. According to Dewey [10], the death rates for patients treated with homeopathy were 1%–2% compared with a 30%–60% mortality for those treated with conventional medicines. Clinical studies have been conducted on Dengue and Acute encephalitis syndrome with homeopathy as an adjunct to usual care in tertiary care setups. In dengue hemorrhagic fever, adjunct homeopathy could bring early improvement in platelet count and a decrease in hospital stay by 2 days [11]. Similarly, in Acute encephalitis syndrome, homeopathy as an adjunct to the institutional management protocol, could decrease the death rate by 15% in comparison to those who received the institutional management protocol only [12]. In both studies, severe adverse effects related to homeopathic medicines were not observed.

At the outbreak of the SARS-CoV-2 pandemic, the Ministry of Ayush,

* Corresponding author.
E-mail address: drdnayak@gmail.com (D. Nayak).

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Government of India, had notified the advisory to use homeopathic medicines in the prophylaxis and management of COVID-19. The advisory recommends giving homeopathic medicines as an adjunct to the standard of care for treatment of the cases [13] in the spirit of the National Health Policy of India-2017 for integrative therapy [14]. This study was undertaken to explore the efficacy of the adjunct homeopathic treatment to the standard of care in the management of COVID-19.

2. Material and methods

2.1. Study design & setting

This was a randomized, placebo-controlled, single-blind study to assess the efficacy of the adjunctive individualized homeopathic medicine in adults (aged ≥18 years) admitted to Chirayu Hospital, a designated COVID-19 treatment, tertiary care hospital in Bhopal, Madhya Pradesh. The ethical clearance was obtained from Central Ethics Committee, Central Council for Research in Homoeopathy, New Delhi (Ref No.1-1/2020-21/CCRH/Tech./23rd EC) and the Institutional Ethics Committee, Gandhi Medical College, and Hamidia Hospital, Bhopal as per the understanding between the hospitals (letter no 13341/MC/IEC/2020). The study was conducted between July 2020 and October 2020. Written informed consent was obtained from each patient before enrolling in the study. This trial was registered in Clinical Trial Registry-India (CTRI/2020/06/026195). The study's protocol has not been published.

2.2. Participants

Patients who were reverse transcription polymerase chain reaction (RT-PCR) positive for SARS-CoV-2 and admitted to the COVID-19 ward of Chirayu Hospital were screened for study eligibility. Symptomatic patients aged 18–80 years, both sexes, willing to give written informed consent were included in the study. However, patients with severe heart, lung, kidney, brain, blood diseases or other important systemic diseases, patients on ventilatory support, immunocompromised patients as evident from medical history, pregnant women and lactating mothers, and also patients considered incapable to complete the study, or not suitable by investigators were excluded from the study. Post-hoc classification of patients was done according to their presentation into mild, moderate, and severe as per prevailing guidelines [15,16].

- *Mild disease*: symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.
- *Moderate disease*: adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including $SpO_2 \geq 90\%$ on room air.
- *Severe disease*: adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or $SpO_2 < 90\%$ on room air.

2.3. Intervention

In the standard of care + homeopathy (SC + H) group, patients were prescribed homeopathic medicine, selected based on the totality of symptoms, and given as an adjunct to the standard of care for COVID-19. However, in some cases, as per requirement, more than one homeopathic medicine was required and used one after another based on relationships between the remedies (complementary medicine, follows well medicines/intercurrent) [17]. Sucrose globules were used as vehicle to administer medicine or placebo to the patients. All the homeopathic medicines were prescribed in the centesimal scale of potencies. The repetition of the medicines was as per the decision of the treating homeopathic physician following the guidelines of homeopathy for centesimal potencies given in the 5th edition of Organon of medicine [18]. Placebo was also repeated following a similar pattern followed for medicine. As an adjunct to the standard of care, patients in the standard of care + placebo (SC + P) group received sucrose globules impregnated with un-succussed dispensing ethyl alcohol (90%, v/v) (placebo). The homoeopathic medicines were procured from Willmar Schwabe, India, a good manufacturing practice-certified pharmaceutical company. The medicine/placebo pills were prepared by the study team (DD, AS, DK, and AK). All patients received supportive care according to the standard of care of the hospital as per the prevailing recommendation of the state government for COVID-19. It consisted of azithromycin 500 mg (once daily), pantaprazole 40 mg (once daily), calcium 500 mg (twice daily), Montelukast 10 mg/Levicetirizin 5 mg (once daily, during hours of sleep), Zinc 50 mg (once daily), vitamin D3 60000 IU (weekly). This regimen of standard care was given for 5 days. However, this protocol was modified as per the requirement and patient prognosis. Medicines were also given for symptomatic management of cough and pain, etc. as per the symptoms of the patient. Anti-hypertensive, anti-diabetic and others were given to patients as per the need of the individual case.

2.4. Outcome measures

The primary outcome of the study was clinical recovery. Clinical recovery was estimated through change in the total symptom score. Each symptom's severity was measured on a 10-point numerical rating patient-reported scale. The patients were asked by the homeopathic treating physicians to rate their symptoms experienced over the past 24 h, 0 being no symptom to 10 being the worst suffering from the symptom imaginable. The score of each symptom was added to get the total symptom score for each patient. The outcome was assessed every day between 8 a.m. and 12 noon.

The secondary outcomes were time to fever clearance and time to clinical recovery. Time to fever clearance was defined as the time from the first dose of the study drug until the temperature dropped to ≤37.5 °C and remained below this temperature for at least 48 h. The body temperature of patients was recorded every 6 h. Time to clinical recovery was the time from enrolment till the total symptom score became '0'.

2.5. Laboratory investigations

As per the hospital's standard procedure, on admission, all patients underwent basic laboratory investigations such as complete blood count, liver function test, kidney function test, lactate dehydrogenase, C-reactive protein, serum ferritin, and high-resolution computed tomography scan of the chest. The follow-up investigations were done for the patients, who did not improve clinically, as per the need of the case.

2.6. Data collection

The clinical data of each patient was recorded systematically on a pre-designed case-recording format for age, sex, duration of fever, symptom severity and resolution, laboratory parameters, date of being COVID-19 positive, exposure and travel history, and others as per the homeopathic case recording format for homeopathic prescriptions. All the data were collected prospectively.

2.7. Sample size

Considering that this was the first research of its kind in homeopathy and COVID-19, and based on the study team's earlier experience, it was expected that 30% of patients in the SC + H group and 14% of patients in the SC + P group would have total symptom score '0' within 10 days of follow-up. With a power of 90%, and an alpha error of 5%, the required sample per group was 139. Assuming a 10% withdrawal rate, a total of 305 patients were needed for enrolment. G-power software available from Heinrich-Heine-Universität, Düsseldorf, Germany was utilized to

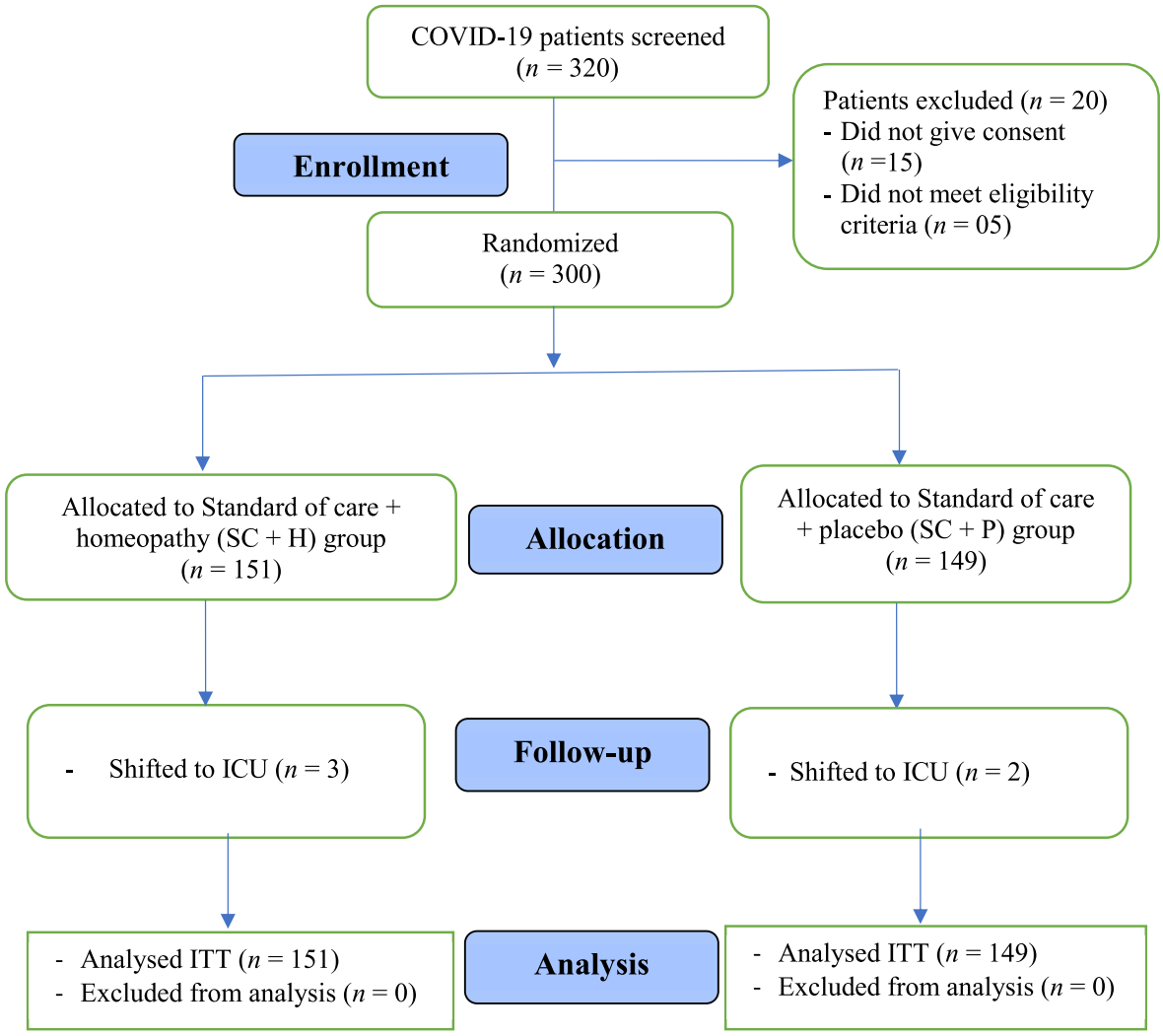

Fig. 1. CONSORT flow diagram of subject progress through the trial. ITT: intention to treat.

compute sample size [19].

2.8. Randomization and masking

Eligible patients were randomly allocated following simple randomization procedures (1:1 allocation ratio) to either the SC + H group or the SC + P group through a computer-generated randomization chart. One of the investigators, JG was responsible for the randomization of the patients. She was not involved in the screening of patients for enrolment. Once a patient was found to be eligible and consented, the screening physician telephonicallycontacted to JG for group assignment. JG kept a record of the name of the patient against the serial no of randomization chart. Treating homeopathic physicians were aware of group allocations, whereas the enrolled participants, conventional physicians, nursing staffs, radiologists, and laboratory personnel were unaware of the study group assignment. The statistician was aware of the group assignment. The overall patient assessment for improvement and discharge was decided by conventional physicians.

The homeopathic medicines were dispensed through medicated sucrose pills; similarly, the placebo group received sucrose pills impregnated with ethyl alcohol. Both medicated and placebo pills were identical in colour, odour, and appearance. The medicine or placebo sucrose pills were given in small vials and consecutively numbered for each participant according to the randomization schedule. In the case of a change of medicine, the vial was replaced with another vial of subsequently prescribed medicine, but the vial had the same number as mentioned in the previous vials. The medicine and placebo were dispensed by the treating homeopathic physicians to the patients.

2.9. Statistical analysis

The quantitative variables were reported as mean ± standard deviations (SD), if they had normal distributions or as median with interquartile range (IQR), if they were skewed. Standard deviation (SD) was used for descriptive statistics and standard error (SE) for inferential statistics. The qualitative ones were reported as numbers (percent). For comparing the quantitative variables, *t*-test or Mann-Whitney test was used. The qualitative variables were compared by a chi-square test. The analysis was performed on an intention to treat basis. For patients who stayed in the hospital for less than 10 days, the last observed status of symptoms was carried forward for analysis. A longitudinal analysis with the main outcome (total symptom score) was carried out using multivariate general linear modeling repeated-measure analysis of variance (GLM-ANOVA) with total symptom score as the dependent variable, treatment assignment, and times of outcome assessment (days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10) as between- and within-subject factors, respectively, and baseline total symptom score as a covariate [20]. Kaplan–Meier curve was used to estimate time to fever clearance and time to clinical recovery and the statistical significance of the difference between the groups was assessed by the log-rank test. The rate of recovery was

Table 1
Baseline characteristics and laboratory data of the participants.

Variables	SC + homeopathy (n = 151)	SC + placebo (n = 149)	P value
Age (mean ± SD, years)	42.54 ± 13.57	41.51 ± 14.27	0.52
Male, n (%)	95 (62.91)	94 (63.08)	0.97
Female, n (%)	56 (37.08)	55 (36.91)	
BMI (mean ± SD, kg/m^2)	25.12 ± 4.76	24.67 ± 5.62	0.57
Days from RT-PCR positive to randomization (median [IQR]) days	1 (1–2)	1 (1–2)	0.05
Days from disease onset to randomization (median [IQR]) days	5 (3–6)	5 (3–6)	0.64
Total symptom score (mean ± SD)	26.73 ± 15.36	17.40 ± 9.29	0.001
Disease severity (n [%])			
Mild	56 (37.08)	73 (48.99)	0.10
Moderate	84 (55.62)	66 (44.29)	
Severe	11 (7.28)	10 (6.71)	
Coexisting conditions (n [%])			
Diabetes mellitus	14 (9.27)	17 (11.40)	0.56
Chronic lung disease (asthma/emphysema/COPD)	5 (3.31)	2 (1.34)	0.25
Hypertension	23 (15.23)	25 (16.77)	0.73
Other disease	11 (7.28)	5 (3.35)	0.12
Vital signs (mean ± SD)			
Pulse (beats/min)	93.65 ± 14.61 (n = 150)	90.03 ± 12.73 (n = 145)	0.02
Respiratory (breaths/min)	19.83 ± 3.25 (n = 132)	18.36 ± 2.10 (n = 137)	0.001
SPO_2 (n [%])			
<90	2 (1.39)	5 (3.54)	0.48
90–95	39 (27.27)	40 (28.36)	
>95	102 (71.32)	96 (68.08)	
Pneumonia (HRCT)			
Present	95 (62.91)	76 (51)	0.03
Absent	56 (37.08)	73 (48.99)	
Symptom presentation (n [%])			
Fever	32 (21.19)	24 (16.11)	0.26
Cough	83 (55.97)	72 (48.32)	0.25
Shortness of breath	59 (39.07)	37 (24.83)	0.008
Myalgia/bodyache	68 (45.03)	66 (44.30)	0.89
Fatigue	84 (55.63)	73 (48.99)	0.25
Headache	68 (45.03)	57 (38.26)	0.23
Sputum Production	33 (21.85)	18 (12.08)	0.02
Diarrhoea	17 (11.26)	10 (6.71)	0.17
Sore throat/pharyngalgia	34 (22.52)	32 (21.48)	0.82
Rhinorrhoea	9 (5.96)	8 (5.37)	0.82
Haemoptysis	1 (0.66)	1 (0.67)	0.99
Chest pain	13 (8.61)	9 (6.04)	0.39
Nausea and vomiting	15 (9.93)	12 (8.05)	0.57
Conjunctival congestion	1 (0.66)	3 (2.01)	0.30
Nasal congestion	6 (3.97)	3 (2.01)	0.32
Chills	18 (11.92)	4 (2.68)	0.002
Throat congestion	13 (8.61)	15 (10.07)	0.66
Tonsil swelling	6 (3.97)	1 (0.67)	0.06
Laboratory parameters at baseline (mean ± SD)			
Haemoglobin (g/dL)	13.46 ± 2.02 (n = 137)	13.78 ± 2.12 (n = 132)	0.20
Neutrophil (cells/μL)	3797.42 ± 2440.21 (n = 151)	3992.81 ± 2438.39 (n = 149)	0.48
Lymphocyte (cells/μL)	1802.15 ± 850.74 (n = 147)	1820.91 ± 893.62 (n = 142)	0.85
Platelet (cells/μL)	273934.78 ± 97212.55 (n = 138)	268977.27 ± 79788.31 (n = 132)	0.64
Haematocrit (%)	46.37 ± 42.66 (n = 136)	43.60 ± 6.07 (n = 132)	0.46
White blood cells (cells/μL)	6913.10 ± 2600.33 (n = 137)	6756.06 ± 2262.43 (n = 132)	0.59
Prothrombin time (s)	13.95 ± 2.15 (n = 123)	14.12 ± 1.82 (n = 127)	0.50
			0.11
Aspartate aminotransferase (U/L)	34.20 ± 22.01 (n = 108)	29.98 ± 15.96 (n = 105)	
Alanine transaminase (U/L)	34.88 ± 27.95 (n = 137)	30.18 ± 29.69 (n = 136)	0.18
Lactate dehydrogenase (U/L)	262.47 ± 89.97 (n = 118)	234.95 ± 78.91 (n = 116)	0.01
Blood urea nitrogen (mg/dL)	22.54 ± 8.22 (n = 136)	21.32 ± 9.82 (n = 136)	0.27
Creatinine (mg/dL)	0.78 ± 0.20 (n = 136)	0.84 ± 0.47 (n = 136)	0.18
Albumin (mg/dL)	4.61 ± 0.52 (n = 136)	4.73 ± 0.66 (n = 135)	0.09
Uric acid (mg/dL)	10.64 ± 3.98 (n = 115)	9.79 ± 4.67 (n = 115)	0.13
C-reactive protein (mg/dL)	19.58 ± 34.39 (n = 137)	12.91 ± 27.71 (n = 133)	0.08
Score as per WHO Ordinal Scale for Clinical Improvement (n [%]) [15]			
3	102 (67.54)	117 (78.5)	0.12
4	38 (25.16)	25 (16.8)	
5	11 (7.28)	7 (4.7)	

BMI: body mass index; COPD: chronic obstructive pulmonary disease; HRCT: high-resolution computed tomography; IQR: interquartile range; RT-PCR: reverse transcription-polymerase chain reaction; SD: standard deviation; SPO_2: oxygen saturation.

calculated as the cumulative percentage of patients becoming symptom free, i.e., the total symptom score becoming zero. Logistic regression was carried out, after adjusting for total symptom score at baseline, for clinical recovery on day 10 of follow-up. The symptoms (dyspnoea, sputum production, fatigue, cough, headache) which were frequently associated with adverse outcomes in COVID-19 patients were analyzed for the percentage of patients getting relieved from them. The day-wise cumulative percentage was calculated for the no. of patients who had resolution of each pathognomonic symptom. A P value less than 0.05 was considered statistically significant. All statistical analyses were carried out using Statistical Package for Social Sciences, version 20.0 (IBM corp., IBM SPSS® Statistics for Windows, Armonk, New York, United States).

3. Results

3.1. Baseline data

A total of 320 patients with RT-PCR positive for SARS-CoV-2 admitted to the hospital were screened for eligibility. Of these, 15 patients refused to participate, 5 patients did not meet inclusion criteria and the remaining 300 patients consented to participate in the study. They were assigned to either SC + H group (n = 151) or SC + P (n = 149). The CONSORT flow diagram of patients in the study is given in Fig. 1.

The mean age was (42.54 ± 13.57) years and (41.51 ± 14.27) years in the SC + H and SC + P groups, respectively. About 63% of patients were of male sex, and the sex-wise distribution of participants was comparable. The most common comorbidity was hypertension followed by diabetes mellitus and chronic lung diseases. At the time of enrolment 62.91% (n = 95) had pneumonia in the SC + H group, while 51% (n = 76) had pneumonia in the SC + P group. Among all the patients, 1.39% (n = 2) had oxygen saturation below 90%, 27.27% (n = 39) had between 90% and 95% in the SC + H group and 3.54% (n = 5) had oxygen saturation below 90%, 28.36% (n = 40) had between 90%–95% in the SC + P group. The patients were classified into mild, moderate, and severe as per the presentation at baseline. The severe (n = 21) patients were comparably distributed between the groups i.e. 7.28% (n = 11) and 6.71% (n = 10) in SC + H and SC + P respectively. 55.62% (n = 84) and 44.29% (n = 66) of moderate patients and 37.08% (n = 56) and

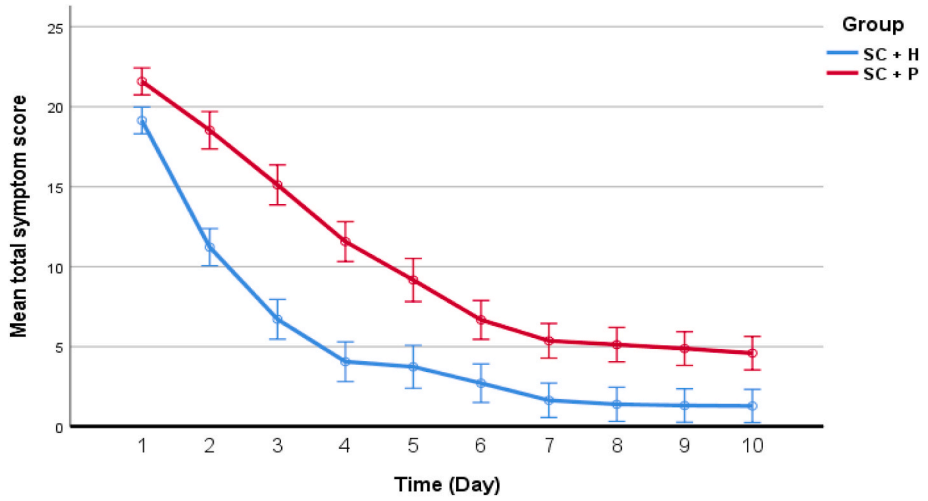

Fig. 2. Comparison of mean total symptom score between the groups over the 10 days follow-up period. Data show estimated marginal mean of total symptom score along with 95% CI [GLM-ANOVA; $F_{(1,\ 297)} = 56.13$, $P = 0.0001$]. SC + H: Standard of care + homeopathy; SC + P: Standard of care + placebo.

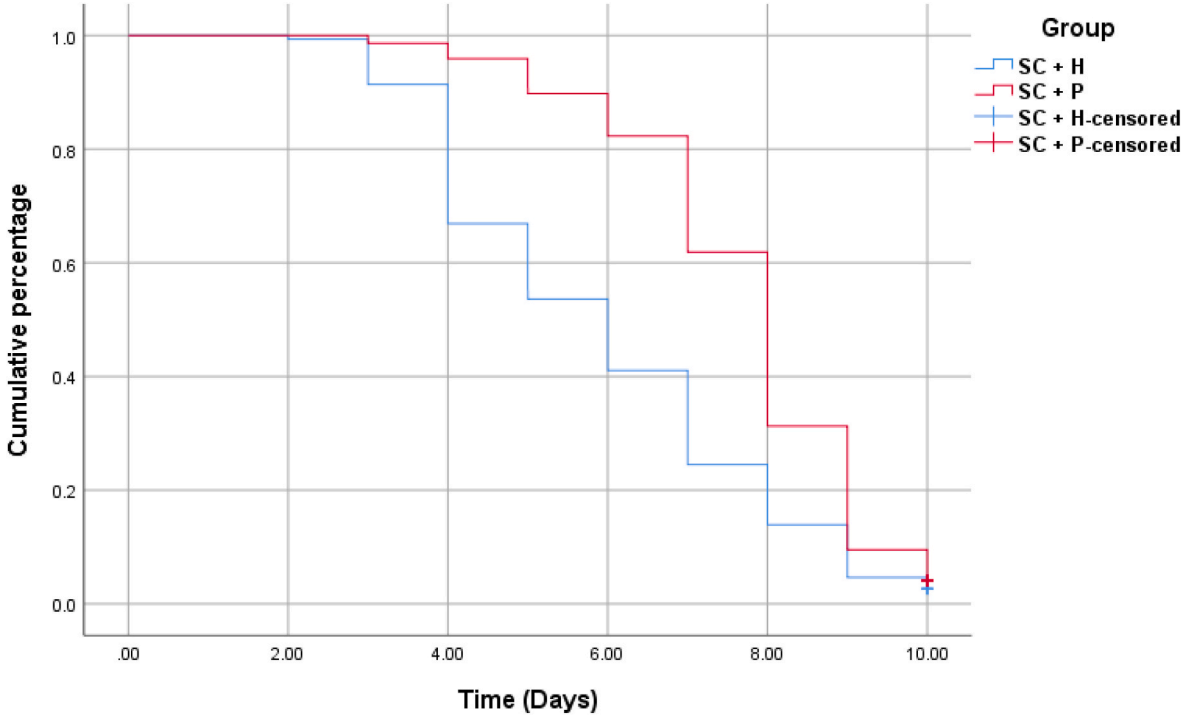

Fig. 3. Kaplan–Meier estimates of time required (days) to clinical recovery. SC + H: Standard of care + homeopathy; SC + P: Standard of care + placebo.

48.99% (n = 73) of mild patients belonged to the SC + H and SC + P groups, respectively. The median time from RT-PCR positive to enrolment to study was 1 day (IQR = 1) in both the groups. The median time from onset of symptoms to initiating treatment was 5 days (IQR = 3) in the groups. The baseline demographic, epidemiological, and clinical characteristics of the patients in the two groups are given in Table 1.

3.2. Change in total symptom score

Multivariate general linear modeling repeated-measure analysis of variance (GLM-ANOVA) was conducted to assess the impact of two different interventions (SC + H, SC + P) on total symptom scores across 10 days follow-up period. There was significant interaction between intervention types and time, Wilks' Lambda = 0.79, $F_{(9,\ 289)} = 8.10$, p = 0.0001, partial eta squared = 0.20. There was a no significant main effect for time, Wilks' Lambda = 0.94, $F_{(9,\ 289)} = 1.80$, p = 0.06, partial eta squared = 0.05). The main effect comparing the two types of intervention was significant, $F_{(1,\ 297)} = 56.13$, p = 0.0001, partial eta squared = 0.13, showing the efficacy of adjunct individualized homeopathy. A comparative trend of decrease in the mean total symptom score of patients is given in Fig. 2.

3.3. Time to clinical recovery

A Kaplan-Meier curve was drawn to compare the time taken for recovery (Fig. 3). We observed that in the SC + H group, time to clinical recovery was about 2 days earlier than that in the SC + P group (SC + H: 5.95 ± SE 0.16 days, 95% CI: 5.63 to 6.27; SC + P: 7.69 ± SE 0.12 days; 95% *CI*: 6.58 to 7.03; $P = 0.0001$).

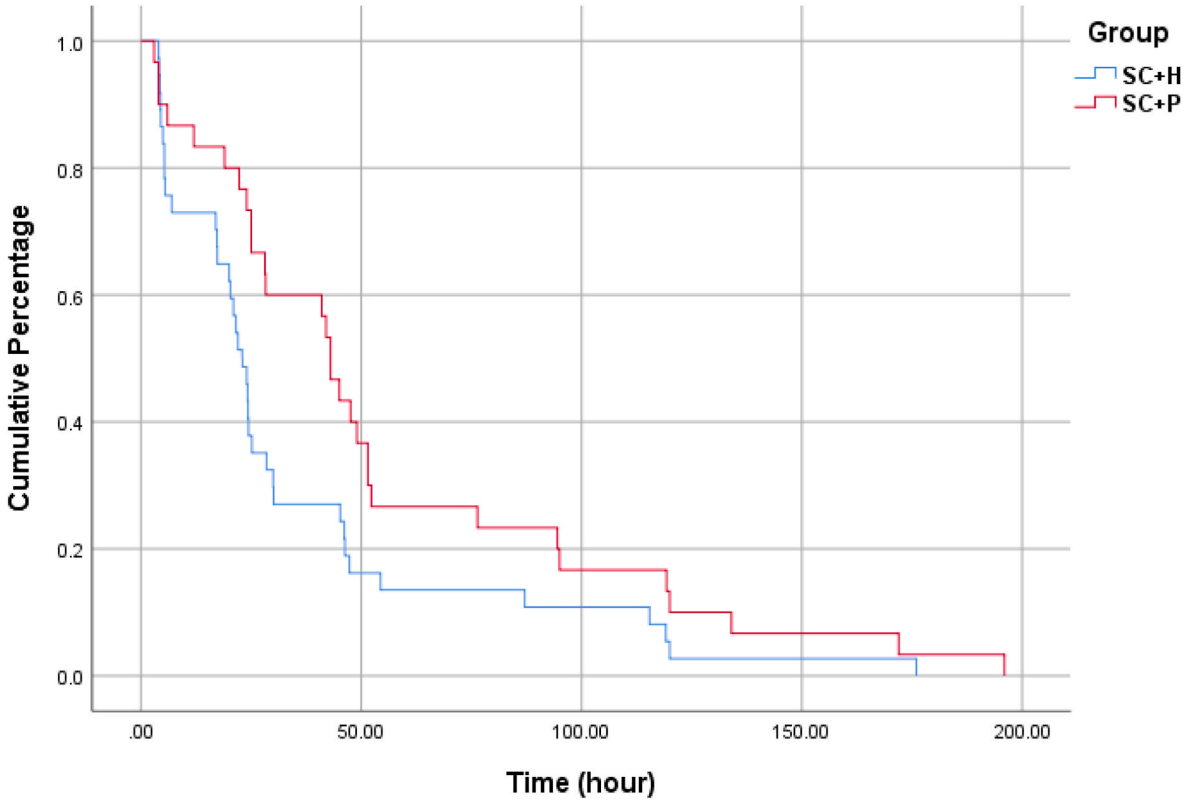

Fig. 4. Kaplan–Meier estimates of time required (hours) for clearance of fever. SC + H: Standard of care + Homeopathy; SC + P: Standard of care + Placebo.

3.4. Time to fever clearance

Fifty-six participants had fever at baseline and another 11 developed fever post-enrolment in the study. A Kaplan-Meier curve was drawn to compare the time taken for the resolution of fever (Fig. 4). We observed that in the SC + H group the resolution of fever was 20 h earlier than in the SC + P group (SC + H: 35.04 ± SE 6.48 h, 95% *CI*: 22.32 to 47.75; SC + P: 55.79 ± SE 9.05 h; 95% *CI*: 38.04 to 73.54; $P = 0.04$).

3.5. Rate of clinical recovery and resolution of pathognomonic symptoms

On day 10 of treatment, 75.50% of patients recovered in homeopathy in comparison to 36.91% in the control group. A graph depicting the trend of recovery between the groups is given in Fig. 5A. A logistic regression carried out showed the odds of patients becoming symptom-free was 8 times higher in the SC + H group than the SC + P group (adjusted odds ratio = 8.36; 95% *CI*: 4.63 to 15.07; $P = 0.0001$).

After 5 days of treatment, a significant number of patients in the SC + H group got rid of symptoms. The cumulative percentage of patients getting relieved of symptoms is as follows (SC + H/SC + P): dyspnoea 60.66%/29.73%; sputum production 85.29%/21.05%; fatigue 68.57%/21.82%; cough 64.63%/33.33%; headache 84.09%/78.13%. The chi-square test indicated that there was significant difference in the proportion of patients in the SC + H group with resolution of dyspnoea ($\chi^2 = 8.72$, $P = 0.003$); sputum production ($\chi^2 = 21$, $P = 0.0001$); fatigue ($\chi^2 = 26.46$, $P = 0.0001$); cough ($\chi^2 = 14.92$, $P = 0.0001$) except headache ($\chi^2 = 0.43$, $P = 0.51$). Time trend graphs depicting the cumulative percentage of patients, who became free from these symptoms over 10 days of follow-up are given in Fig. 5. B–F.

3.6. Medicines, potency and change of prescription

Forty homeopathic medicines were prescribed for the patients. Of these, *Arsenicum album* was prescribed to 9.93% patients ($n = 15$), *Bryonia alba* and *Phosphorus* were to 7.94% ($n = 12$) patients each; *Rhus toxicodendron* to 6.62% ($n = 10$); *Natrum muriaticum* ($n = 9$, 5.96%); *Hepar sulphuricum & Pulsatilla nigricans* ($n = 7$, 4.63% each); *Lycopodium clavatum & Nux vomica* ($n = 6$, 3.97% each); *Belladonna*, *Carbo vegetabilis*, *Chininum arsenicum*, *Gelsemium* ($n = 5$, 3.31% each). At first prescription 44.37% ($n = 67$) of patients received 30C potency, 47.68% ($n = 72$) received 200C potency and the remaining 7.94% ($n = 12$) received higher potency. Of all, 63% ($n = 96$) patients received one homeopathic medicine only, while 36.42% ($n = 55$) patients required two or more homeopathic medicines during the study period.

3.7. Adverse effects

An adverse effect was observed in 1.6% ($n = 5$) of patients who were shifted to ICU support; of which 1.98% ($n = 3$) from the SC + H group, and 1.34% ($n = 2$) from the SC + P group. Among the 2 patients from SC + P group, one had uncontrolled blood sugar and the other patient had a non-responsive fever. Out of 3 patients of SC + H, one had severe dehydration with bedsores, one had a non-responsive fever, one had fluctuating oxygen saturation. No deaths were reported from both groups.

4. Discussion

Our study found that adjunct individualized homeopathic medicine with the standard of care significantly improves clinical recovery with early resolution of symptoms compared to those who received placebo along with the standard of care. This study is the first of its kind with adjunct individualized homeopathic treatment of COVID-19.

As the pandemic progressed and more people recovered from COVID-19, it was realized that post-COVID symptoms were a healthcare burden. About 82% of post-COVID-19 patients reported suffering from at least one symptom related to COVID-19 [21]. In our study in the standard care group, 63% had at least one symptom at the time of

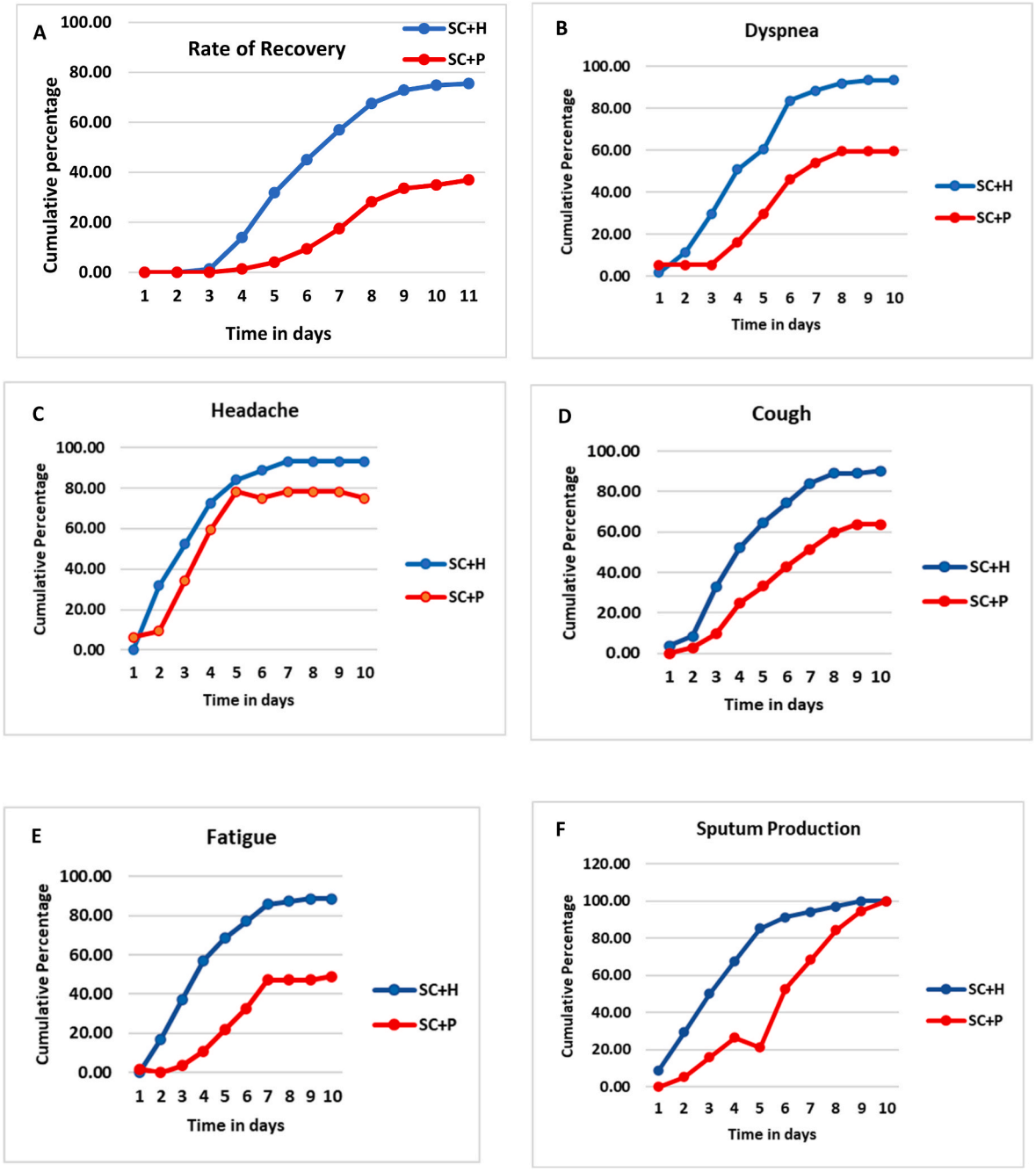

Fig. 5. Rate of Clinical recovery and resolution of pathognomonic symptoms of COVID-19. A. Rate of Clinical Recovery B. Dyspnoea; C. Headache; D. Cough; E. Fatigue; F. Sputum production. Data presented as cumulative frequency. SC + H: Standard of care + homeopathy; SC + P: Standard of care + placebo.

discharge from the hospital. However, in the adjunct treatment group, only 24% of patients had any residual symptom related to COVID-19 at discharge from the hospital.

Adjunct homeopathy could significantly shorten the time for fever clearance, thereby reducing the need for antipyretics. It has been reported that symptoms such as dyspnoea, sputum production, fatigue, and headache are frequently observed in patients with fatal outcomes [22]; however, in our study, these symptoms resolved earlier in patients who received adjunct homeopathy than in those who received standard of care only. It is observed that patients in the SC + H group required fewer antipyretics and other medications for symptom relief.

In our study, we found that *Arsenicum album, Phosphorus,* and *Bryonia* were the most prescribed medicines. It corroborated with the findings of physicians of Italy [23], though not a systematic study. Similar findings were reported by *Michael* et al. [24] regarding useful remedies. These medicines are also highly recommended in homeopathic literature for illnesses with similar presentations like Influenza. In the absence of specific anti-virals, adjunct homeopathy can be a boon for the management of COVID-19 patients in an integrative approach. Homeopathy may be studied as a standalone therapy in cases of mild and moderate cases in future studies. Adjunct homeopathic management of patients on standard of care can be beneficial not only in early recovery and better clinical outcomes but also in the prevention of complications. Similar encouraging results of the integrative approach were evident in infectious diseases like Dengue [11], Acute encephalitis syndrome [12], etc.

Resolution of pneumonia could not be assessed due to non-availability of follow-up chest CT/HRCT. However, symptoms related to pneumonia were resolved earlier in the SC + H group than in the SC +

P group. Nonetheless, objective evidence of the resolution of pneumonia seems to be more appropriate. In our study, we did not estimate the viral load and the time to its clearance. It will be of interest to see the virus clearance in relation to clinical improvement following homeopathic medication.

Due to the large number of COVID-19 patients during the study at the hospital, the follow-up laboratory tests of all the patients could not be done due to a resource crunch. Future studies may estimate the changes in laboratory parameters. However, this does not limit the applicability of the study results as clinical improvement is evident from an early resolution of symptoms of the patients. Restricted access to patients due to high transmission of COVID-19 infection is also a limitation for homeopathic prescriptions; because, to select homeopathic medicine, various attributes of patients are essential along with the disease features.

Various inflammatory markers have been identified as prognostic indicators for COVID-19. Future studies may target to study the effect of homeopathic medicine on these markers and ultimately on cytokine storm [25]. Our study being a single-blinded trial, has its limitation due to experimenter bias, as the physicians responsible for the group allocation and homeopathic treatment were aware of the group assignment. Further, the primary outcome of our study was a patient-rated subjective score, hence, there is the possibility of bias favouring the treatment group [26], however, the patients were not aware of the group assignment. In spite of the randomized allotment of patients to the groups, our study had differences between groups for total symptom score at baseline, no. of patients having pneumonia, and few other parameters. However, the no. of moderate/severe (based on the presence of pneumonic changes in the lung) cases and patients having higher total symptom scores at baseline were more in the SC + H group. Further, it is suggested that future studies need to consider stratified randomization based on the severity of the illness to achieve balanced groups.

Keeping in view the evolving understanding of disease and treatment, the team was allowed to conduct the single-blinded study by the COVID-19 task force of the Ministry of Ayush. Further, due to limited access to patient and stressed health care during the pandemic, limited logistics and treating physicians getting infected with COVID-19, implementing a double-blind study might have been difficult. Future studies may be planned as double-blind to avoid experimenter biases. The standard of care protocol also evolved with the progress of the pandemic. So, the treatment outcome of later guidelines may be different than the standard of care provided in this study.

Serious adverse events were not observed in this study. The beneficial effect of this integrative approach refutes the possibility of drug-to-drug interaction. This also fulfills the vision envisaged in the National Health Policy of India for integrative management of diseases [14].

5. Conclusion

Adjunctive individualized homeopathic management with an integrated standard of care has resulted in better clinical outcomes in patients with COVID-19 in terms of early recovery. Further, double-blind, controlled studies are needed to confirm these results.

Author statement

Debadatta Nayak, Anil Khurana conceptualized the study and developed the protocol. Juhi Gupta, Krishna Gopal Singh, Abhijeet Deshmukh, Deblina Das, Abhishek Saha, Deepak Kumar, Ashwini Kumar, and Sanjay Gupta were responsible for data collection. Ajay Goenka, SK Mishra, and Anil Khurana oversaw the study implementation and provided resources. Debadatta Nayak and Anupriya Chaudhary were responsible for overall project administration and coordination with the team at the study site for data collection. Debadatta Nayak and Anupriya Chaudhary analyzed the data. Debadatta Nayak drafted the first version of the manuscript with relevant suggestions from the authors. All the authors approved the version submitted for publication.

Declaration of competing interest

The authors declare no conflict of interest.

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