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A randomized placebo controlled clinical trial using Homoeopathy as an adjuvant to standard care in the management of COVID-19☆

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ABSTRACT

Background: COVID-19 challenged medical fraternity with high transmission rates, lack of prior sensitization of the immune system, high mortality, and emotional stress due to fear of death and social isolation.
Objective: The objective of this trial was to test the effectiveness of individualized homoeopathic treatment as an adjuvant to modern medicine.
Design: setting, participants, and interventions
This was a randomized, double-blind, placebo-controlled trial. Two hundred and sixty-nine participants who tested positive for COVID-19 infection (N Gene, ORF 1-ab-Gene, and the S Gene of the SARS COV-2 virus) were randomized into two parallel groups. A total of 133 participants (49 %) were randomized to the homeopathic group. The remaining 136 (51 %) patients in the control group received a placebo intervention in addition to standard care of modern medicine.
Main outcome measures: The endpoints of the trial were measuring the impact on patient symptoms, mortality rate, need for mechanical ventilation, inflammatory markers, and length of hospital stay. Statistical analysis was performed using a multivariate random effects model for symptoms and inflammatory markers. Logistic regression models were used to assess clinical outcomes, including intensive care unit (ICU) requirement, ventilator support, and deaths.
Results: Of the 269 participants, 133 (49 %) were in the homoeopathic group and 136 (51 %) were in the control group. There were no significant differences in the demographic characteristics, comorbidities, or allopathic treatment administered within the groups at baseline. The median scores for shortness of breath, cough, weakness, and fatigue significantly reduced on days five and ten. There were no significant differences in the median values of inflammatory markers. The ICU requirement ($p = 0.01$), ventilator requirement ($p = 0.01$), and mortality ($p = 0.003$) were significantly lower in the homoeopathic group.
Conclusion: Homoeopathy as an adjuvant to standard care in the management of COVID-19 resulted in lowering of clinical symptoms, and a significantly lower ICU requirement, requirement of ventilation, and mortality rate compared to standard care alone.

☆ Trial Registration Number: The interventional trial (CTRI/2020/04/024925) was approved and has been completed.

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1. Introduction

COVID-19 in India was a component of the global coronavirus disease pandemic of 2019, which was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of March 18, 2022, India had the second-highest number of COVID-19 confirmed cases worldwide, with more than 43 million recorded cases and 516,281 fatalities [1]. Approximately 86 % of patients with COVID-19 predominantly have respiratory tract disease; however, some progress to a more severe and systemic disease characterized by Acute Respiratory Distress Syndrome (ARDS), septic shock, and multi-organ failure, including acute kidney injury and cardiac injury [2]. The primary pathology of COVID-19 is endothelial damage to the vasculature, micro vascular thrombosis, and haemorrhage. It is associated with extensive alveolar and interstitial inflammation in the lungs, hypercoagulability of the blood, and refractory ARDS. According to autopsy findings in China and some European countries, a coagulation cascade may also be triggered by hypoxemia caused by ARDS. Chronic COVID-19 complications, including long-COVID-syndrome, brain fog, extreme weariness, pain, trouble thinking, and dizziness, are also evident [3].

The conventional therapy initially employed to treat COVID-19 patients included a combination of antipyretics such as paracetamol, acetylsalicylic acid, antimalarials (hydroxychloroquine), steroids (dexamethasone), antibiotics, and antiviral medications with or without non-invasive or invasive respiratory support, depending on the patient's specific indications [4]. The desired effects of the treatment were inhibition of virus replication, anti-platelet aggregation, anti-inflammatory, and anti-lung injury. The major goal of treatment is to minimize host cell damage caused by any inflammatory immune cascade activation, decrease the cytokine storm, and immunomodulation for faster viral load clearance [5]. However, more recent treatments such as monoclonal antibodies and antiviral compounds are either in use or in the clinical development stage [6].

Homoeopathy is a holistic healing method developed by Hahnemann in 1796. It is based on the concept that diseases can be treated with medications in minute dosages capable of eliciting similar symptoms in healthy people (called similia similibus curentur, or "like cures like''). When a drug is diluted, a process known as "potentization" makes it stronger; frequently, pharmaceuticals are highly diluted outside the purview of molecular biology [7–10]. Homoeopathy can slow the progression of disease by preventing over-activation of the immunological cascade, which in turn can affect gene expression, cytokine induction, and the host immune response [11–13]. Individualized homoeopathy is a comprehensive approach to patient care that considers a patient's clinical presentation, pathology, individual emotional responses, physiological attributes, past diseases that may indicate comorbidities, and premorbid health evaluation. Treatment consists of administering a single indicated homoeopathic medication that complements the patient's diseased state [7,14].

There is considerable historical evidence of homoeopathy being employed as an adjuvant or stand-alone treatment during epidemics. Infectious disorders, such as scarlet fever, smallpox, cholera, diphtheria, malaria, yellow fever, Spanish flu, chikungunya, acute encephalitis syndrome, leptospirosis, and H1N1 infection, have been the subject of numerous reports that have highlighted the effectiveness of homoeopathy [10,15–19]. Several case studies from Hong Kong have reported the successful use of individualized homoeopathy for COVID-19 based on clinical symptoms [20]. Homoeopaths in Asia, especially India, have attempted to utilize homoeopathy for COVID-19, but not consistently or with a detailed assessment of treatment. [21], Thus, with this background, we conducted the present randomized trial to compare the effectiveness of individualized homoeopathic therapy (intervention group) as an adjuvant treatment (as per govt policy) to standard care versus placebo plus standard care treatment (control group) for COVID-19.

2. Materials and methods

2.1. Trial design

A double-blind, randomized, multicentre, placebo-controlled clinical trial was conducted using homoeopathy as an adjuvant to the standard care.

2.2. Participants

2.2.1. Eligibility criteria for participants

COVID-19 patients presenting to any of the aforementioned hospitals were screened for enrolment in the study. The inclusion criteria were as follows.

1. Male and female patients aged between 18 and 80 years.
2. Patients who tested positive for COVID-19 infection (N Gene, ORF 1-ab-Gene, and the S Gene of the SARS COV-2 virus) using the reverse transcription polymerase chain reaction test (RT-PCR Test) on material collected through nasopharyngeal and oro-pharyngeal swabs.
3. Patients with mild to moderate disease presentation without evidence of viral pneumonia or hypoxia.
4. Moderate cases with clinical presentation with a record of SpO2 $\geq$ 90 % and who were only on non-invasive respiratory oxygen support.
5. Patients who could provide written informed consent to participate in the study.

The following patients were excluded from the study: pregnant and lactating women, patients on ventilator support, severe and critical cases, immune-compromised patients, patients with a history of malignancy on active chemotherapy and radiation, those with active autoimmune disorders, and patients with cardiac conditions (ischemic heart disease, cardiomyopathies with congestive cardiac failure, or arrhythmias).

2.2.2. Settings and locations

The study participants were enrolled at four tertiary care hospitals (in-patient departments) in Pune, Maharashtra, India, from May 2020 to October 2020. Includes a diverse group of 16 medical professionals with expertise in homeopathy, medicine, and related fields. (11) homoeopathic consultants, (4) specialists from internal medicine, and (1) specialist in clinical research. The KEM Hospital Research Centre, Lokmanya Medical Research Centre, Ruby Hall Clinic, and Yashwantrao Chavan Memorial Hospital were the study sites and designated COVID-19 care centers located in the city of Pune, in the state of Maharashtra, in the west of India. The study was approved by Institutional ethics committee (IEC) [Date of approval – 21 April 2020, PS-38–040].

2.3. Interventions

2.3.1. Treatment administration

The medicines were procured from Doliosis, SBL, Schwabe, Dr. Reckeweg, and St. George's homoeopathic manufacturing units. Medicines were prepared according to Hahnemannian serial dilution method of manufacture (multi-flask method) based on Homooepathic Pharmacopeia of India (HPI) and German Homoeopathic Pharmacopeia (GHP). The selected single homoeopathic medicine was then administered to the patients in the homoeopathic group in the appropriate potency and frequency, as decided by the Principal Investigator (PI). The dilutions utilized in this study included 30 CH, 200 CH, 1 M, and 10 M. The planned frequency of consultations was two per day, and this target was achieved without any deviations. Additionally, it should be noted that the prescription required agreement between two homeopaths, and the process involved expert consultation. The homoeopathic doctor reported to the PI regarding each patient's clinical progress, based on

which PI would modulate, according to Homoeopathy Principles, the individualized homoeopathic treatment. If the patient did not improve or developed new symptoms, Homoeopathic medication was changed.

Allopathic doctors, as site investigators, would also modulate allopathic treatment based on the standard of care guidelines and clinical progress of the disease. The same standard of care was provided to all the patients enrolled in both groups in the study. The types of allopathic medications and their proportionate distributions are shown in (Table 1.)

2.3.2. Placebo administration

The placebo was composed of unmedicated pills prepared from cane sugar. Individualized homoeopathic medication and placebo were indistinguishable from each other as they were similar in shape, size, texture, taste, and packing, with similar code indicators.

The same clinical care protocol was used for both groups. All patients in the placebo group underwent the same protocol of daily visits and evaluation by treating physicians. As in the treatment arm, if the patient did not improve or developed new symptoms, the placebo was "replaced."

2.4. Outcomes

The primary outcome measure was the change in symptom severity scores (shortness of breath, cough, weakness, and fatigue) from baseline to days 5 and 10. Secondary outcome measures included changes in inflammatory marker levels from baseline to days 5 and 10, the proportion of patients requiring oxygen therapy, the duration of oxygen requirement, the duration of hospital stay, the proportion of patients requiring ICU admission, the proportion of patients requiring ventilatory support, and the mortality rate.

2.4.1. Assessment and outcomes

The baseline data was collected on the day of recruitment. A detailed history was collected on a pre-designed structured clinical record form to maintain uniformity in the data capture. This included demographic and behavioral/contact information (international travel, contact with a patient with COVID-19 infection, health care worker), presence of comorbidities, and other medical history. The physician also assessed general symptoms, such as appetite, thirst, fever, and perspiration. A record of any treatment received in the community outside the study site for COVID-19 symptoms before admission to the study was maintained.

In addition, a visual analogue scale (0−10) was used to assess parameters such as cough, breathlessness, myalgia, fatigue, chills, anosmia, lassitude, abdominal pain, and diarrhoea. These parameters were assessed in all patients. The treating physician showed the VAS scale to each patient and recorded the patient-indicated scores. SpO2 levels were measured, and the need for oxygen, type of delivery for oxygen, and amount required were also recorded. A list of all allopathic medicines administered to the patient during the entire course of observation and management was maintained.

Patients were investigated at baseline, on days 5 and 10 for the following parameters: complete blood count, liver function tests, renal function tests, and sodium and potassium levels. In addition to these investigations, tests for other markers such as C-reactive protein (CRP), D Dimer, interleukin-6 (IL-6), and serum ferritin were also carried out. A baseline chest radiograph was taken up and repeated according to the clinical indications. All clinical, laboratory, and radiological parameters were shared daily with PI. The PI used this real-time information to adjust or change medication (dose/quantity) in the homoeopathic group. A similar protocol was followed for the placebo group as discussed above. All subjects were advised to follow a routine diet and hygiene according to the trial site's policy during the entire study period. After completion of the study and discharge of the patient from the study site, all participants were asked to stop trial medications and take the advice of the treating physician for further management.

The protocol for revisions in prescriptions of the homoeopathic medicines was as follows: after administering the selected doses of the first medicine determined on the day of admission, for two days, if there was no perceptible improvement (as measured by the scoring system for each subjective symptom) and/or if any new symptoms had subsequently emerged in the patient, we increased the potency or frequency of administration of the first medicine. If this was ineffective, a second medicine was administered to the patient after the withdrawal of the previous medicine. Sometimes, it was necessary to identify and administer a third medicine if the patient's symptoms persisted or changed. The above protocol ensured that every chosen homoeopathic medicine administered to the patients conforms to the totality of symptoms. Decisions related to treatment initiation and changes thereafter were made by PI alone. The treating physicians and patients remained blinded to the medicine and changes thereafter.

Drug compliance was assessed by the treating physician and was reported daily to the PI. Patients who continuously missed their medicine doses for three consecutive days or missed more than nine doses during the study period were withdrawn from the study and designated as dropouts.

The endpoints for the study were: 1) day of discharge or a maximum of 10 days of treatment; 2) the patient, after enrolment, developed the need for and was administered invasive respiratory support through an endotracheal tube and a ventilator; and 3) death of the patient.

The investigators analyzed four main types of outcomes in the study:1) clinical symptoms (scores for cough, shortness of breath, fatigue, and weakness as assessed using the VAS score); 2) biochemical parameters, including inflammatory markers (D Dimer, CRP, lactate dehydrogenase [LDH], serum ferritin, interleukin-6 [IL-6]); 3) oxygen requirement (whether required or not, how many days was it required, requirement per day, and average requirement over the entire duration of observation); and 4) other clinical outcomes: duration of stay, required admission to the intensive care unit (ICU) (yes/no) (this was decided by the treating physician based on features such as clinical symptoms, oxygen saturation, tachypnea, hypotension), required a ventilator (yes/no) (this was also decided based on the clinical response and parameters), and death. Potential adverse events reported during the study period were also recorded.

Table 1
Comparison of total number of different allopathic medications between the two groups.

Characteristics	Total	Treatment group	Control group	P value[a]
Antibiotics	183 (68.0)	90 (68.2)	93 (67.9)	> 0.99
Antipyretics	73 (27.1)	37 (28.0)	36 (26.3)	0.79
Antivirals	178 (66.2)	84 (63.6)	94 (68.6)	0.39
Steroids	166 (61.7)	81 (61.4)	85 (62.0)	0.91
Anti-parasitic	27 (10.0)	12 (9.1)	15 (11.0)	0.61
Anticoagulants	177 (65.8)	86 (65.2)	91 (66.4)	0.83
Proton pump inhibitors	184 (68.4)	91 (68.9)	93 (67.9)	0.85
Supplements	210 (78.1)	107 (81.1)	103 (75.2)	0.24
Other symptomatic	123 (45.7)	65 (49.2)	58 (42.3)	0.26

p value < 0.05 was taken as statistically significant.
[a] Using Chi squared test

2.5. Sample size calculation

As the study was conducted early in the pandemic, the investigators did not have any pilot data to base the sample size estimation. Furthermore, the guidelines for the management and prophylaxis of COVID-19 have changed according to existing and emerging evidence. Thus, for this trial, it was initially proposed to include 100 patients each in the homoeopathic and control groups. Since some dropouts were expected, we attempted to screen 300 patients so that approximately 120 patients would still be eligible for inclusion in each group. After

including 120 patients in each group, even if 15 % dropped out during the trial period, 100 patients in each group could be included in the final analysis.

2.6. Randomization

A consecutive sample of eligible patients who fulfilled the inclusion criteria were enrolled in the study. After enrolment, patients were randomized into a homeopathic or placebo group using a computer-generated simple randomization process. The pre-generated randomization codes were placed in sealed, opaque envelopes that were sequentially numbered and only opened after patient enrollment. Randomization was performed at the hospital level. Details of the total number of patients from each hospital are presented in (Fig. 1). The randomization sequence was maintained by the PI and the pharmacist, who were the only individuals aware of the treatment allocation. Furthermore, investigators assessing outcomes had no access to the randomization sequence, preventing selection bias and ensuring true concealment of allocation.

Allopathic therapy was based on ongoing updates to the recommendations of the Indian guidelines. Each trial site comprised of a homoeopathic and allopathic doctor who monitored and observed the patients daily. Both allopathic and homoeopathic clinical care providers were blinded to patient allocation. The individualized homoeopathic medication and placebo were indistinguishable from each other as they were similar in shape, size, texture, and taste and were packed with similar code indicators.

2.7. Blinding procedure

Once a patient was recruited, an investigator from the team in the respective hospital was assigned the case. The investigator was blinded to patient allocation. The investigator assessed and examined patients according to the trial protocol. The Principal Investigator (PI) had access to all clinical case records daily. The investigator reported it to the PI. The PI initiated and modulated the treatment based on the investigator's report. The randomization chart was available to the pharmacist and the PI. After the recruitment of a new COVID-19 patient, based on the randomization list and in coordination with the PI, the pharmacist prepared the package to be administered to the patient in addition to allopathic medication.

The pharmacist prepared similar packaging for both medications under the supervision of the PI. This package was then handed to the treating physician. Medication was administered by the treating physicians according to the instructions. The treating physician at the site was responsible for patient compliance with the treatment. Daily patient reviews were conducted through interviews, symptom grading, and physical examinations in both groups to monitor clinical progress.

2.8. Statistical methods

The normality of continuous data was assessed using the Shapiro–Wilk test. The investigators estimated the mean and standard deviations (SDs) or the medians and interquartile range (IQR) for continuous data. Similarly, the proportions of categorical data were estimated. The means between two groups were compared using the *t*-test (paired or unpaired, depending on the nature of the comparison). The medians between the two groups were compared using the Mann-Whitney test. Per-protocol analysis was used in the present study. Per-protocol analysis was chosen over ITT as homeopathy requires individualized prescriptions, making it difficult to define a minimum dose for ITT inclusion. Incomplete adherence could have been misinterpreted as treatment failure. Additionally, the primary endpoint was subjective and binary in nature, rendering imputation methods like LOCF unsuitable.

Multivariate analysis was performed for the following outcomes: symptoms (scores for cough, shortness of breath, and fatigue), inflammatory markers (CRP, D-dimer, and LDH), and other clinical outcomes (ICU required, ventilator required, and deaths). For the first six outcomes (symptoms and inflammatory markers), random-effects models for multivariate analysis were used. These models are useful for the repeated measurement of data and account for both within-individual and between-individual variances. The investigators used observations at baseline, day 5, and day 10 for the random effects models. Logistic regression models were used for the next three outcomes (clinical outcomes). The investigators initially built the null model, followed by crude estimates for each variable. Finally, a complete model was built using all the explanatory variables in the same model. Demographic variables, comorbidities, modern medicine given, oxygen requirement, and smoking status were included as potential confounders in the multivariate models. Investigators tested the interaction terms for the type of group (treatment or control) and the day of observation of

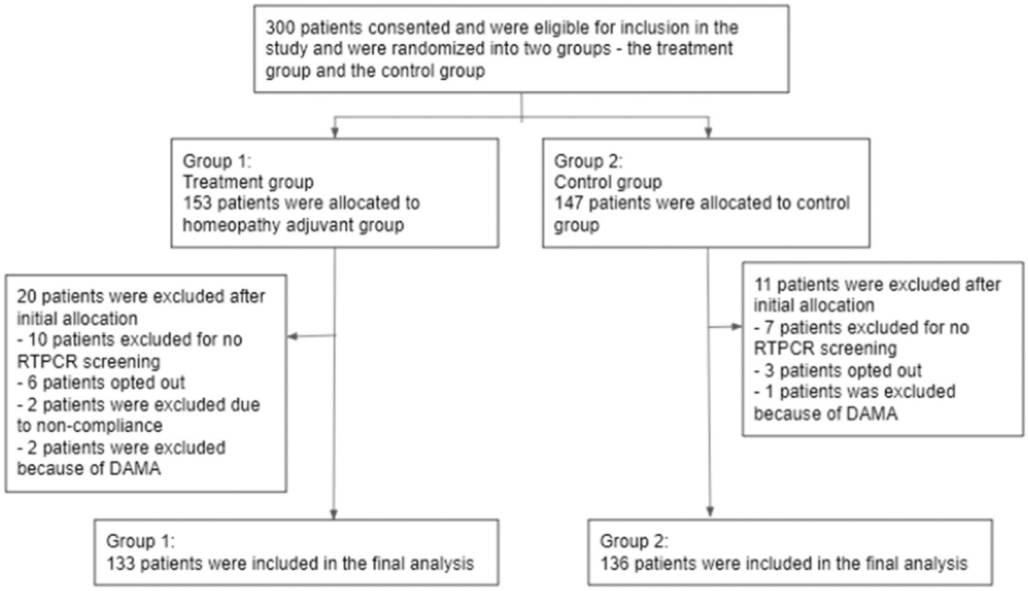

Fig. 1. Recruitment of study participants.

symptoms and inflammatory markers. The fit of the models was assessed using the Akaike Information Criteria and Bayesian Information Criteria.

The trial data had missing values for the study variables. The investigators did not impute any missing data. The main variables for which there were more than 10 % missing data were D Dimer, IL-6, CRP, serum ferritin, and LDH. Since investigators used linear random-effects models for these outcomes, the estimates obtained using these models accounted for the missing values for those patients in whom these outcome measures were not available.

2.9. Reporting guidelines

The study is reported in accordance with CONSORT and RedHot guidelines.

3. Results

3.1. Baseline characteristics

Of the 269 patients, 133 (49 %) were in the homoeopathic group, and 136 (51 %) were in the control group. The mean age (SD) of the participants in the treatment and control groups was 47.9 (13.9) and 50.9 (13.6) years, respectively; the difference was not statistically significant ($p = 0.07$). Although the proportion of male patients (74 %) was higher than that of female patients (26 %), the difference in sex distribution was not statistically significant across both groups ($p = 0.75$). The most common comorbidities were diabetes mellitus (29 %) and cardiovascular diseases (26 %). No significant differences were observed in the proportion of comorbidities between the treatment and control groups (Table 2). Standard care included prescriptions for antibiotics (68 %), antivirals (66 %), steroids (62 %), anticoagulants (66 %), proton pump inhibitors (68 %), and supplements (78 %). There were no significant differences in these medications' use between the study and control groups. Among the remedies, *Bryonia* was the most frequently prescribed, with 29 prescriptions (12.78 % in the first, 6.02 % in the second, and 3.01 % in the third prescriptions). This was followed by *Arsenicum Album*, with 25 prescriptions (12.78 %, 5.26 %, and 0.75 %, respectively), and *Pulsatilla*, with 22 prescriptions (12.03 %, 3.76 %, and 0.75 %). *Camphora* accounted for 21 prescriptions (9.02 %, 3.76 %, and 3.01 %) (Supp Table 1). The cumulative doses across the prescriptions demonstrated minimal variability. The mean dose for the first prescription was 20.77 ± 7.28, followed by a marginal increase to 21.00 ± 12.51 in the second prescription. The mean dose then slightly decreased to 20.00 ± 8.53 in the third prescription. These findings reflect a consistent dosing pattern with minor fluctuations across successive prescriptions. The distribution of potencies revealed a preference for higher dilutions. 200 CH was prescribed in 64 prescriptions (48.12 %), while 1 M was used in 62 (47.37 %) patients. 10 M was prescribed in 4 (3.01 %) and 30 CH in 1 (0.75 %) patients respectively. These results demonstrate the predominant use of higher potencies in the treatment regimen. The demographic characteristics, comorbidities, and allopathic treatment administered to the treatment and control groups are described in (Tables 1, 2 and Suppl. Table 1).

Table 2
Table showing the baseline demographic characteristics and comorbidities in 269 COVID-19 patients, in Pune, Maharashtra, India.

Characteristics	Total	Treatment group	Control group	P value
All	269 (100.0)	133 (49.4)	136 (50.6)	
Demographics				
Age				
Mean (SD)	49.4 (13.8)	47.9 (13.9)	50.9 (13.6)	0.069[a]
Sex				
Male	200 (74.3)	97 (73.5)	103 (75.2)	0.75[b]
Female	69 (25.8)	35 (26.5)	34 (24.8)	
Comorbidities				
Chronic Lung Disease	11 (4.1)	5 (3.8)	6 (4.4)	0.81[b]
Diabetes Mellitus	79 (29.4)	36 (27.3)	43 (31.4)	0.46[b]
Cardiovascular diseases	70 (26.0)	35 (26.5)	35 (25.6)	0.86[b]
Chronic renal diseases	7 (2.6)	2 (1.5)	5 (3.7)	0.45[b]
Chronic liver diseases	1 (0.4)	0 (0.0)	1 (0.7)	> 0.99[b]
Neurological diseases	2 (0.7)	1 (0.7)	1 (0.7)	> 0.99[b]
Other diseases	11 (4.1)	3 (2.3)	8 (5.8)	0.22[b]
Smoker	9 (3.4)	6 (4.6)	3 (2.2)	0.33[b]

[a] Calculated using Students *t*-test
[b] Calculated using Chi-squared test

3.2. Outcome assessment

There was no significant difference in the median scores (IQR) for shortness of breath (6 [3,8] vs. 6 [4,8]; $p = 0.58$), cough (5 [2,6] vs. 4.5 [2,6]); $p = 0.89$), weakness (6 [4,8] vs. 5 [3,8]; $p = 0.10$), and fatigue (3 [0,6] vs. 3 [0,6]; $p = 0.81$) between the treatment and control groups at baseline. In both groups, the median scores for each of these symptoms significantly reduced on days five and ten. The median and IQRs for each symptom at baseline, on day five, and day ten are presented in (Table 3). As shown in (Table 3), in general, there were no significant differences in the median values of the inflammatory markers (for whom the values were available) between the treatment and control groups. Although the median values of some markers changed on days five and ten, the pattern and significance were not consistent. Nonetheless, there was no significant difference in the values of these markers between the treatment and control groups, even on days five and ten.

Although the proportion of patients who required oxygen was lower in the homoeopathic group, the difference was not statistically significant (64 % vs. 72 %, $p = 0.13$) (Table 4). Similarly, the median number of days in which oxygen was required was not significantly different between the treatment and control groups. The details of the oxygen requirements in both groups are provided in (Table 4).

There was no significant difference between the homeopathic intervention and control groups in the median duration of hospital stay (9.5 [8, 12.5] vs. 10 [9,13]; $p = 0.25$) (Fig. 2).

The proportion of COVID-19 patients requiring ICU admission was significantly lower in the homoeopathy group (5.3 % vs. 14.6 %, $p = 0.01$). Furthermore, the proportion of patients who required a ventilator was significantly lower in the homoeopathic group than in the non-homeopathic group (2.3 % vs. 9.5 %, $p = 0.01$). Finally, the number of deaths was significantly lower in the homoeopathic group (0.8 % vs. 8.8 %, $p = 0.003$) (Table 4). A total of 13 Grade 5 (fatal) serious adverse events resulting in death were reported, with 1 occurring in the treatment group and 12 in the control group. None of these events were related to the study interventions. Additionally, one patient from the placebo group experienced three Grade 3 serious adverse events, including dyspnea, stroke, and elevated blood pressure, all of which were deemed unrelated to the study medications.

3.3. Multivariate analysis

As discussed earlier, investigators used multivariate models for three types of outcomes (symptoms, inflammatory markers, and clinical outcomes).

For symptoms, after adjusting for demographic variables and other potential confounders, as described earlier, it was observed that over the 10-day-period, the mean cough score (-0.08, 95 % confidence interval [CI]: −0.40, 0.23, $p = 0.60$), shortness of breath score (-0.07, 95 % CI: −0.45, 0.30, $p = 0.70$), and fatigue score (-0.09, 95 % CI: −0.53, 0.36, $p = 0.69$) were lower in the homoeopathic group; however, this difference was not statistically significant. The day of observation (days 5 and

Table 3
Table showing the symptom score and biochemical parameters at baseline, day 5, and day 10 in 269 COVID-19 infected patients, Pune, Maharashtra, India.

	Group	Baseline	Day 5	Day 10
		Median (IQR)	Median (IQR)	Median (IQR)
Symptom scores				
Cough	Treatment	5 (2, 6)	0 (0, 1)***	0 (0, 0)***
	Control	4.5 (2, 6)	0 (0, 1)***	0 (0, 0)***
p value†		0.89	0.16	0.09
Shortness of breath	Treatment	6 (3, 8)	0 (0, 1)***	0 (0, 0)***
	Control	6 (4, 8)	0 (0, 2)***	0 (0, 0)***
p value†		0.58	0.12	0.31
Fatigue	Treatment	3 (0, 6)	0 (0, 0)***	0 (0, 0)***
	Control	3 (0, 6)	0 (0, 1)***	0 (0, 0)***
p value†		0.81	0.08	0.06
Weakness	Treatment	6 (4, 8)	0 (0, 1)***	0 (0, 0)***
	Control	5 (3, 8)	0 (0, 2)***	0 (0, 0)***
p value†		0.10	0.24	0.09
Biochemical parameters / Inflammatory markers				
C-Reactive Protein	Treatment	9.9 (3.6, 32.2)	2.1 (0.5, 5.3)***	3.2 (0.9, 8.9)***
	Control	12.4 (4.8, 42)	2.9 (0.9, 9.1)***	4.3 (1, 14.0)***
p value†		0.34	0.02	0.26
LDH	Treatment	337 (269, 458)	281 (230.6, 366.9)***	329.3 (246.9, 416.3)
	Control	356 (279, 474)	313.8 (241, 403.4)***	315.8 (243.1, 428.8)
p value†		0.35	0.16	0.83
Ferritin	Treatment	279.0 (121, 547.1)	290.4 (133.2, 540.3)	264.5 (110.4, 468.6)**
	Control	290.9 (134.5, 505.7)	263 (122.6, 495.8)	167.3 (109.5, 424.3)***
p value†		0.84	0.42	0.09
D-Dimer	Treatment	260 (198, 346)	250 (150, 400)	223.5 (27, 524.5)
	Control	308 (212, 636)	342 (194.6, 616.4)	209.8 (1.25, 488.5)***
p value†		0.01	0.03	0.69
IL−6	Treatment	38.6 (12.8, 88.9)	5.2 (1.1, 15.8)**	4.9 (1.6, 20.9)
	Control	25.5 (11.9, 67.7)	8.8 (3.9, 42.2)	8.2 (5.1, 35.8)
p value†		0.68	0.16	0.27

* $p < 0.05$,
** $p < 0.01$,
*** $p < 0.001$ All these are based on comparison with the value for that time (day 5 or 10) with baseline
† All the p values for this table were calculated using Mann-Whitney Wilcoxon's ranksum test

10) was significantly associated with a reduction in the scores for all three symptoms. The interaction terms for the group and day of observation were not significant in any of the models.

For inflammatory markers, after adjusting for demographic variables and other potential confounders, it was observed that, over the 10-day-period, the mean CRP levels (-4.04, 95 % CI: −10.44,2.35, p = 0.22), D-dimer levels (-120.87, 95 % CI: −367.51, 125.78; p = 0.34), and LDH levels (-41.59, 95 % CI: −89.21, 6.02, p = 0.09) were lower in the homoeopathic group; however, this difference was not statistically significant. In general, the day of observation was significantly associated with a reduction in these markers levels. The interaction terms for the group and day of observation were not significant in these models. In these clinical outcomes, after adjusting for demographic and other potential confounders, including comorbidities and modern medicine

Table 4
Oxygen requirement, ICU and ventilator requirement, and deaths in the 269 study patients.

Characteristics	Total	Treatment group	Control group	P value
	N (%)	n (%)	n (%)	
All	269 (100.0)	133 (49.1)	136 (50.9)	
Oxygen				
Required – Yes	183 (68.0)	84 (63.6)	99 (72.3)	0.13[a]
Number of days				
Median (IQR)	3 (0, 6)	3 (0, 6)	4 (0, 7)	0.17[b]
Total oxygen required (L/min)				
Median (IQR)	20 (0, 60)	12 (0, 61)	22 (0, 57)	0.29[b]
Average oxygen required (L/min)				
Median (IQR)	7.8 (5, 13.2)	8.6 (5, 13.8)	7.3 (5, 13)	0.65[b]
Other outcomes				
ICU admission required - Yes	27 (10.0)	7 (5.3)	20 (14.6)	0.01*,[a]
Ventilator required - Yes	16 (5.9)	3 (2.3)	13 (9.5)	0.01*,[a]
Death	13 (4.8)	1 (0.8)	12 (8.8)	0.003*,[a]

* P value < 0.05 considered statistically significant
[a] Calculated using Chi squared or Fisher's exact test for low expected cell counts
[b] Calculated using Mann-Whitney Wilcoxon's ranksum test

treatment, it was observed that ICU requirement was significantly lower in the homoeopathic group (OR:0.32, 95 % CI:0.12, 0.90, p = 0.03). In addition, the requirement for a ventilator was also significantly lower in the homoeopathic group (OR: 0.22, 95 % CI:0.05, 0.89, p = 0.034). Finally, mortality was significantly lower in the homoeopathic group (OR: 0.04; 95 % CI:0.01, 0.47, p = 0.01). The odds ratios and 95 % CIs for the logistic models are presented in (Table 5). There were no adverse events attributable to the medication in the homoeopathic group, and the patients tolerated this medicine well.

4. Discussion

To our knowledge, this clinical trial was one of the first to register as a study in the Clinical Trial Registry of India to assess the effectiveness of homoeopathic treatment as an adjuvant in COVID-19 infection. The trial results indicated that patients in the homoeopathic group were less likely to require admission to the ICU and requirement for a ventilator. The proportion of deaths was also significantly lower in the homoeopathic group compared to other arm. Furthermore, the proportion of individuals with oxygen requirements was lower in the homoeopathic group. Finally, clinical symptoms and inflammatory markers were lower in the homoeopathic group over the 10-day observation period, although all these differences were not statistically significant. Overall, outcomes appeared to be better in the homoeopathic group.

A similar study conducted in Mumbai with a sample size of 124 participants demonstrated a statistically significant impact on the death rate and oxygen requirement in the homoeopathic group; however, the nature of statistical analysis (univariate or multivariate) is unclear [22]. In another similar study carried out in Pune, India, a sample size of 100 subjects, whose data were analyzed through univariate analysis, showed similar results of reduction in oxygen requirements in the homoeopathic group. The homoeopathic group also showed reduced hospital stay [23].

The current trial was conducted relatively early during the pandemic period. Pune, the city where the trial was conducted, was one of the few cities with many cases during this phase of the pandemic. This trial studied an integrated system of care (allopathic and homoeopathy) for the management of patients with COVID-19. Minimal observer bias was achieved through blinding of the treating physicians and the absence of direct PI involvement. In this trial, a range of outcomes were studied,

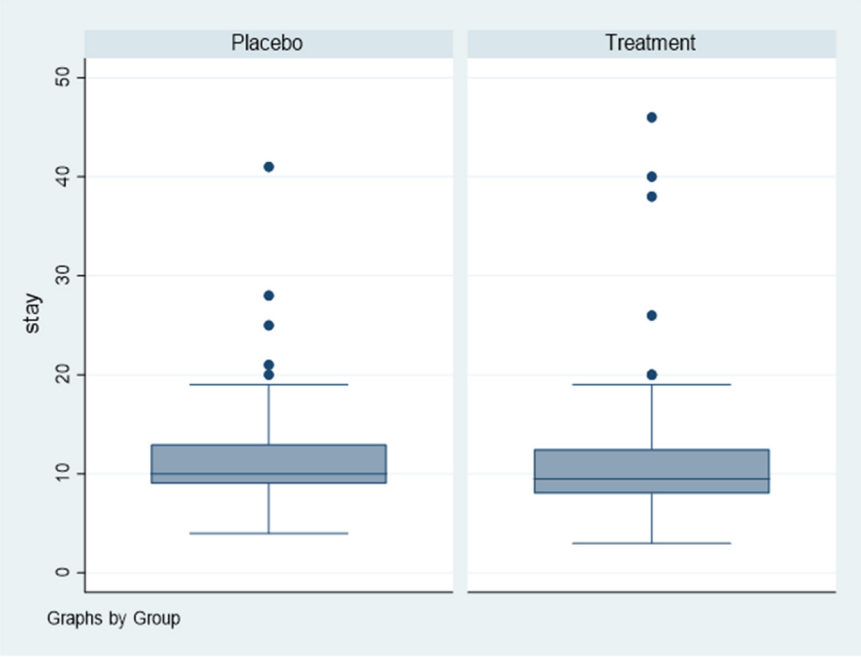

Fig. 2. Graph showing the duration of stay in 269 COVID-19 infected patients.

Table 5
Logistic regression models for ICU admission, ventilator requirements and mortality in the study patients.

ICU*	Odds ratio	95 % CI		p value	Ventilator**	Odds ratio	95 % CI		p value	Death***	Odds ratio	95 % CI		p value
Group					Group					Group				
Placebo	Ref				Placebo	Ref				Placebo	Ref			
Treatment	0.32	0.12	0.90	0.03	Treatment	0.22	0.05	0.89	0.034	Treatment	0.04	0.01	0.47	0.01
Age	1.07	1.03	1.11	0.001	Age	1.08	1.02	1.15	0.007	Age	1.13	1.04	1.23	0.004
Sex					Sex					Sex				
Male	Ref				Male	Ref				Male	Ref			
Female	1.60	0.53	4.84	0.40	Female	0.42	0.09	2.08	0.29	Female	0.23	0.03	1.71	0.15
Oxygen- Yes	1.59	0.39	6.42	0.52	Oxygen- Yes	2.14	0.24	19.4	0.50	Oxygen- Yes	2.10	0.17	25.3	0.56
Comorbidities					Comorbidities					Comorbidities				
Lung	0.47	0.04	5.31	0.54	Diabetes M	0.89	0.26	3.04	0.86	Diabetes M	1.73	0.41	7.28	0.46
Diabetes M	1.06	0.40	2.85	0.91	CVD	1.18	0.34	4.12	0.79	CVD	1.47	0.33	6.47	0.61
CVD	0.44	0.12	1.35	0.15	CKD	0.56	0.01	38.3	0.79	CKD	0.29	0.01	46.4	0.63
CKD	0.47	0.01	32.8	0.73	Neurological	53.9	0.56	> 100	0.09	Neurological	> 100	1.04	> 100	0.049
Neurological	35.5	0.36	> 100	0.13										

$P < 0.05$ considered statistically significant

They were also adjusted for allopathic treatment such as antivirals, immune-suppressants, steroids, antibiotic, antipyretic, anticoagulant, anti-parasitic, and supplements.

Diabetes M- Diabetes mellitus, CVD- Cardiovascular disease, CKD- chronic kidney disease

* Other comorbidities could not be included in this model, for comorbidities -the reference category is no comorbidities;

** Lung and other comorbidities could not be included in this model, for comorbidities -the reference category is no comorbidities;

*** Lung and other comorbidities could not be included in this model, for comorbidities -the reference category is no comorbidities,

including clinical symptoms, laboratory investigations, oxygen requirement, and other clinical outcomes (such as the requirement of an ICU, ventilator, and death). Of these, the clinical scores were a subjective assessment by the patients themselves, whereas management-related issues (ICU, ventilator, and oxygen requirements) were decisions taken by the treating physician based on the daily clinical condition of the patient. Since neither the patients nor the treating physicians were aware of the group (intervention or control), the investigators potentially minimized bias in the measurement of these outcomes. Comorbidities and the standard care with allopathic medicines administered to each patient, which were not considered during patient randomization, were adjusted using the random effects models of multivariate analysis [24].

Several trials with a similar research design were conducted in allopathy to evaluate new drugs or repurpose old ones. A double-blind, randomized, placebo-controlled study of the effect of early treatment with Ivermectin in patients with COVID-19 reported that Ivermectin did not lead to a lower frequency of medical admission to a hospital due to COVID-19 progression or prolonged emergency department observation [25]. Similarly, in another randomized controlled trial to study the efficacy and safety of two neutralizing monoclonal antibody therapies, Sotrovimab and BRII-196 plus BRII-198, in adults hospitalized with COVID-19, it was observed that neither Sotrovimab nor BRII-196 plus BRII-198 demonstrated efficacy in improving clinical outcomes in patients hospitalized with COVID-19 [26]. Another randomized, double-blind, placebo-controlled, multicenter trial to study the effect of Remdesivir in adults with severe COVID-19 observed that Remdesivir was not linked to statistically significant clinical benefits in adult

patients hospitalized for severe COVID-19 [27]. Thus, the results of this study provide more hope than the other medical interventions under investigation.

India has a unique distinction from adopting an integrative approach to COVID-19. This strategy was supported by the Ministry of Health and Family Welfare and the Ministry of AYUSH. The AYUSH Ministry, which is responsible for Ayurveda, Yoga, Naturopathy, Unani, Siddha, Sowa-Rigpa, and Homoeopathy systems of medicine, facilitated clinical trials using an integrative approach [28]. Based on similar lines, this trial was conducted to assess whether individualized homoeopathic treatment as an adjuvant to standard care is safe and efficacious in patients hospitalized with COVID-19. A patient-centric integrative treatment approach was adopted in this trial in conventional modern medicine hospitals. The findings of this trial indicate that the safety and benefits of using an integrative approach in COVID-19 outweigh its risks. This approach may be useful for the integrative management of COVID-19 patients in various centers across the country.

This trial helped establish the role of individualized homoeopathy as an adjuvant treatment in COVID-19 management. Individualized homoeopathic treatment comprises eliciting the clinical presentations, state of pathology, individual emotional responses, personalized physiological attributes, past illnesses indicating comorbidities, and an assessment of the premorbid state of health, to arrive at a totality of symptoms, which leads to the selection of a single indicated homoeopathic medicine that matches the above totality [29]. Homoeopathy modulates host immunity through the psycho-neuro-endocrine-immune axis model to combat disease and helps restore normal physical and mental health [30]. Individualized homoeopathic treatment is customized, a person-specific treatment designed for that, one sick individual. To clarify, in this trial, a homoeopathic medicine was not used as an anti-COVID-19 or antiviral, but as an individualistic therapeutic agent aimed at improving the overall quality of the outcomes in these patients. As seen in the data, this form of management was possibly useful in COVID-19 patients and significantly reduced the requirement for invasive ventilation and hence the death. This was at a time when the evidence around allopathic medicine for COVID-19 was continuously evolving, sometimes with contradictory findings resulting in poor consensus among physicians for the best available treatment for COVID-19 [31,32].

This study had certain limitations. One of the limitations of this trial was that IL6, a marker for inflammation [33], was not included as a mandatory marker in the trial protocol. Although we encouraged the treating physicians to test for inflammatory and other biological markers, most of these were based on the current burden on patients in the hospital and the need for tests to manage the patient. Thus, there were missing values for all these outcomes. The investigators did not use any methods to impute the values for this missing data. The data was modelled based on the existing values only. The study also did not include high-resolution computed tomography of the chest as a mandatory component of the management in the protocol, due to financial constraints. Furthermore, the study did not standardize the allopathic treatment in the intervention or control groups. The treating physician prescribed these medications based on current evidence (this was early on during the pandemic) and guidelines. It is likely that these guidelines may have changed over time. However, this concern was addressed by using random effects multivariate analysis, thereby adjusting for the above variables. For these reasons, this study may be considered a pragmatic trial. Nonetheless, the trial highlights that homoeopathic medicine in sub-atomic form and allopathic medicines in molecular form can be safely used together under the watchful supervision of the respective clinicians [34,35].

5. Conclusion

The integrated treatment, as observed in this study, improved the clinical outcomes in patients with COVID-19 without causing any side effects. An integrative approach based on the application of fundamental principles can be safely used to treat COVID-19 and similar infections. Similar multi-centric studies with larger sample sizes that address some of the limitations of this trial should be conducted in the future to validate the findings of this study. Furthermore, trials using homoeopathy as an adjuvant may be considered for seasonal community-acquired viral pneumonia in non-pandemic scenarios.

Consent for publication

Not applicable. The manuscript does not contain data from any individual person.

Ethical statement

Ethics Committee Name: Poona Medical Research Foundation, Institutional Research Committee.

Office Address: E4C to E4F Fourth Floor, Fifth Avenue Condominium, Dhole Patil Road, Pune-411001.

Approval Date: 21.04.2020

Number: PS-38–040

Statement: Approval is granted for a period of 1 year from the date of approval.

The Principle Investigator must submit in writing an application for continuation of

Approval within 1 month prior to expiry of approval.

Written informed consent was obtained from participants prior to the study.

The written informed consent was obtained in English and/or Hindi (National Language).

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.aimed.2025.100502.

Data availability

All data are fully available without restriction. All relevant data are within the manuscript and its supporting information files. Any additional data/information can be made available by Principle Investigator after a due permission from member secretary of Institutional Ethics Committee.

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