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# Investigating the effectiveness of PHR-160 spray in controlling and improving the symptoms of patients with covid-19 - A multicenter, double-blind, randomized clinical trial study

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## Abstract

**Background:** One of the recommended treatment methods for covid-19 is herbal treatments, which, if used, can be used as an effective preventive or supportive treatment in the treatment plan of patients with covid-19. PHR160 spray is a combination of cineole, menthol, Safran, safranal, and crocin each of these substances affects respiratory diseases alone.

**Aim:** Investigating the effectiveness of PHR-160 spray, in the treatment of Covid-19.

**Methods:** The present study is a multicenter, double-blind, randomized clinical trial study, which was conducted in 4 medical centers. The study population includes all hospitalized patients with covid-19 who met the study inclusion criteria. The data collection tool was a checklist including 1- demographic information, 2- vital signs, symptoms, CT scan changes, and drug side effects (neural, cardiac, and respiratory) at the beginning of admission and from the first to the 10th day.

**Result:** There was no significant difference between the intervention and control groups in the study of demographic variables, vital signs, symptoms, CT scan changes, and drug side effects before using PHR-160 spray (P>0.05). Also, after using PHR-160 spray for ten days, there was no significant difference in the admission to the intensive care unit, and patient mortality in the two groups (P>0.05)

**Conclusion:** Based on the results, PHR-160 spray has no beneficial effects in controlling the symptoms of patients with covid-19 and cannot play an effective role in improving the patient's condition and reducing the complications caused by the disease.

**Keywords:** PHR-160 spray, Covid-19, treatment, patient.

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## Background

Covid-19 is a disease with multi-organ involvement and a wide range of manifestations[1]. After the emergence of this disease in December 2019, preventive measures such as the use of vaccines and treatment such as the use of many antiviral drugs were investigated, which helped to contain and control the disease to some extent. Of course, despite the extensive efforts at the world level to find a definitive treatment, this issue is still an important and unfinished challenge. In the meantime, one of the recommended treatment methods, along with other treatments used, is herbal treatments, which, if used, can be used as an effective preventive or supportive treatment in the treatment plan of patients with covid-19[2,3]. Also, researchers are facing another challenge regarding providing a definitive treatment until the complete eradication of Covid-19, and that is the access of low-

income geographical and economic areas to effective treatments[4].

Studies have shown that the use of Chinese herbal medicine alone can treat mild cases of Covid-19 and improve the effects of standard treatments without causing side effects. According to the studies, unique effects are expected for each of the effective substances used in traditional medicine, which are usually extracted as essential oils. For example, cineole leads to a reduction in the deterioration of chronic obstructive pulmonary disease (COPD)[5], long-term treatment of airway inflammation in bronchial asthma[6], anti-inflammatory activity in asthma, control of airway mucus concentration by inhibition of cytokine[7], treatment of Acute Nonpurulent Rhinosinusitis[8], Anti-inflammatory and antioxidant function, treatment of nasal congestion and nasal secretions and reduction of ventilator-dependent pneumonia in patients undergoing mechanical ventilation. Menthol is effective in the treatment of sore throat, coughs related to colds or respiratory infections[9], treatment of nasal congestion caused by inflammation of the nasal mucosa and relieving the symptoms of shortness of breath[10], treatment of mild asthma[11] and treatment of asthma, bronchitis, colds (in the form of fumigation), influenza and other respiratory diseases as well as It is effective to relieve nasal congestion in children. In in vivo studies, Crocin has a protective effect on allergic asthma in rats[12] and can lead to a reduction in respiratory tract inflammation[9] and a reduction in lipopolysaccharide-induced acute respiratory distress syndrome[12]. In the field of in vivo studies, safranal prevents lung inflammation[14] and can relieve asthma[15]. Safran plays a role in treating asthma and improving the function of the respiratory system, pulmonary obstruction, pulmonary inflammation, and trachea-related responsiveness in animal models and has antitussive[16], anti-inflammatory[17], anti-human immunodeficiency virus (HIV) and anti-Herpes Simplex Virus (HSV) effects[18].

Essential oils are a mixture of volatile oily compounds and are made as a secondary metabolite in medicinal plants, and they have many potential biological and pharmacological activities, including antimicrobial, antioxidant, anti-inflammatory, and anti-cancer properties without adverse effects on consumption. They are envisioned and have many applications in the pharmaceutical and food industries. Therefore, the present study is conducted to investigate the effectiveness of PHR-160 spray, which is a combination of the mentioned effective substances, in the treatment of Covid-19.

## Method

The present study is a multicenter, double-blind, randomized clinical trial study with ethics code IR.BMSU.REC.1398.387 and clinical trial registration code IRCT20200731048257N1 in Iran's clinical trial registration center, which was conducted in 4 medical centers. The study population includes all hospitalized patients with covid-19 who met the study inclusion criteria.

### inclusion criteria

It includes confirmed infection with Covid-19 according to Polymerase Chain Reaction (PCR) test results, ground glass appearance in low-dose CT scan, arterial oxygen saturation of less than 93%, and complaints of shortness of breath.

### Exclusion criteria

including patients with HIV, patients with cancer undergoing chemotherapy, patients with immune diseases receiving immunomodulator drugs, patients requiring hospitalization in the intensive care unit, patients with uncontrolled heart, kidney, or liver failure, and women who were pregnant or was during breastfeeding.

### Randomization and blinding

In this study, the sampling method was available and to assign the patients to two intervention and control groups, the block randomization method (Permuted Balanced Block Randomization) was used with the size of random blocks of 4 and 6, because of the use of this method Concealment of the randomization sequence has also been observed. Also, a unique code was generated for each person, and the drugs were labeled using the mentioned codes and provided to the centers, and a total of 330 patients who entered the study were randomly assigned to the intervention group (165 patients) and the control group (165 patients).

In this study, the patients, the research staff, and the treatment staff were unaware of the allocation of patients to two intervention and control groups. To blind the patients, a placebo was used, which was prepared by the drug manufacturing company and to blind the research team and the treatment staff, unique codes and completely similar packages were used for blinding

### Data collection

The data collection tool was a checklist including 1-demographic information, 2- vital signs, disease symptoms, CT scan changes, and drug side effects (neural, cardiac, and respiratory) at the beginning of admission and from the first to the 10th day. The checklist of this study is based on the article of Solaymani-Dodaran et al[19].

**Intervention**

The participants in addition to the standard treatment including (Hydroxychloroquine + Azithromycin + Naproxen + Prednisolone) according to the type of grouping (intervention and control), received PHR-160 spray and placebo for 10 days and in the form of 1 puff up to 10 times a day .This procedure was determined by a council consisting of an internal specialist, infectious disease specialist, pharmacotherapy specialist, and emergency medicine specialist.

**Sample size**

The number of sample volumes was calculated using G-Power3.1.9.7 software. Considering the error level of 5%, the power of the test is 90%, the effect size is 0.2, and considering the 5 times of measurement of the main variable, oxygen saturation percentage in both intervention and control groups, as well as the correlation coefficient of 0.7 for two consecutive measurements, The necessary sample volume was determined 330 people (with considering the possible loss of about 10%).

**Statistical analysis**

The main analysis approach in this study was "intention to treat". If there was a deviation from the protocol for any reason, the result information was collected as much as possible until the end and considered in the analysis stage. In the end, the results of the analysis with the per protocol approach were also extracted and compared with the results of the first approach. First, a descriptive analysis of the variables in the study was done. To ensure the correctness of the random assignment, all variables (patient characteristics including demographic information) before the start of the intervention (baseline) were compared in two groups. Considering the superiority approach of this study, the percentage of special care receiving needs in each of the groups was compared and a statistically significant difference was reported. Drug side effects were also compared in two groups. After providing 50% of the samples, an interim analysis was performed and the result was presented to DSMB and the alpha error value was corrected based on statistical considerations. Due to the difference in the prognosis of the patients depending on the presence of comorbidity and age and gender, subgroup analysis was performed for these people. In this study, a safety and data monitoring committee were formed from the beginning of the study with the participation of the following people who were responsible for approving the protocol and obtaining informed consent:

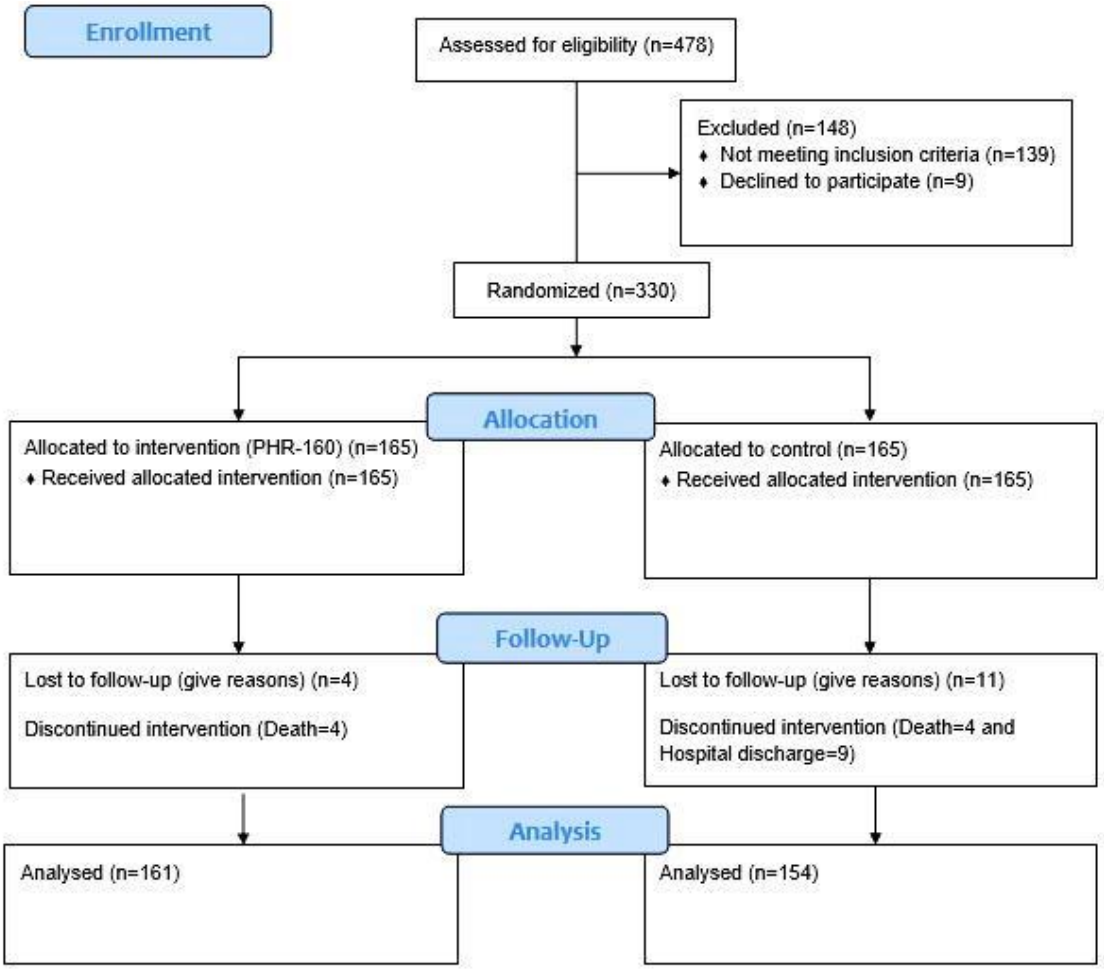
1. A lung or infectious disease specialist or clinical pharmacist with sufficient experience in the treatment of Covid-19
2. An epidemiologist with sufficient experience in the methodology of clinical trial studies
3. A statistician

Initially, this committee was formed once a week and while listening to the report of the results obtained from the prescription of drug protocols, they examined all the unwanted adverse events including serious adverse events and all cases of death, and found the cause. The monitoring of unwanted injuries was of particular importance in this study.

Descriptive statistics including mean, standard deviation, frequency, and percentage were used to describe the condition of control and intervention groups. Also, data were analyzed using an independent t-test and chi-square test. A generalized estimating equation (GEE) model with an exchangeable correlation matrix for repeated measures was used to compare the groups, adjusted for other covariates such as age, BMI, and sex. $P < 0.05$ was considered significant.

**Ethical considerations**

The research units were given the right to participate in the research. Also, patients could withdraw from the study at any time if they did not want to continue participating in the study.




**Flowchart 1.** Consort Flow Diagram

## Results

We screened 478 patients; 330 were eligible and 315 were enrolled (Flowchart 1). 161 people (51.1%) were in the intervention group and 154 were in the control group, and the average age of the study participants was 51.37 ± 13.72. Other demographic characteristics are shown in Table 1.

**Table 1.** Other demographic characteristics

| variable | Mean ± SD |
|---|---|
| Height | 168.58±9.89 |
| Weight | 81.31±15.46 |
| BMI | 28.63±4.81 |
| Duration of hospital stay | 2.61±4.76 |

There was no significant difference between the intervention and control groups in the study of demographic variables, vital signs, disease symptoms, CT scan changes, and drug side effects before using PHR-160 spray (P>0.05). Also, after using PHR-160 spray for ten days, there was no significant difference in the admission to the intensive care unit, and patient mortality in the two intervention and control groups (P>0.05). (Table 2)

**Table 2.** Comparison of mortality rate and hospitalization in the intensive care unit in two intervention and control groups

| Variable \ Group | | Control Abundance (percentage) | Intervention Abundance (percentage) | p-value |
|---|---|---|---|---|
| **Mortality** | Yes | 0.9(1) | 5(4.3) | 0.21 |
| | No | 106(99.1) | 111(95.7) | |
| **Hospitalization in the ICU** | Yes | 4(3.6) | 6(5.1) | 0.75 |
| | No | 106(96.4) | 111(94.9) | |

After using PHR-160 spray for ten days, there was no significant difference in patients' vital signs (body temperature, heart rate, breathing rate, systolic blood pressure, diastolic blood pressure, and oxygen saturation percentage), CT scan changes and disease symptoms (chest pain chest, cough, headache, respiratory discomfort, shortness of breath, abdominal pain, anorexia, diarrhea, fatigue, joint pain, smell disorder, chills, sore throat, taste disorder, and nausea and vomiting) in the intervention and control groups (P >0.05). (Table 3), but the statistical modeling test by adjusting the effect of gender, age, and BMI showed that the chance of having muscle pain in patients who used the spray was significantly lower (P = 0.02) than in other patients (figure 1).

**Table 3.** Comparison of mean vital signs in two intervention and control groups

| Group / Variable | Control Mean ± SD | Intervention Mean ± SD | p-value |
|---|---|---|---|
| Body temperature | 36.76±.72 | 36.78±.84 | 0.81 |
| heartbeat | 86.87±14.07 | 89.18±12.56 | 0.12 |
| Breathing rate | 17.63±1.51 | 17.41±1.26 | 0.17 |
| Systolic BP | 121.07±15.00 | 120.99±12.28 | 0.95 |
| Diastolic BP | 77.05±11.14 | 76.25±10.42 | 0.51 |
| Oxygen saturation percentage | 92.58±3.94 | 92.03±4.27 | 0.22 |
| Cough(days) | 1.03±0.73 | 1.1±.63 | 0.38 |
| Cough (nights) | 0.69±0.77 | 0.75±0.88 | 0.52 |
| Shortness of breath | 1.68±0.66 | 1.81±0.76 | 0.1 |

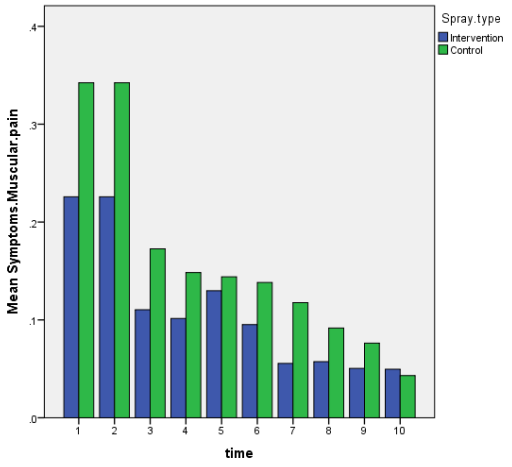



**Figure 1.** The effect of duration of using PHR-160 spray on muscular pain in two intervention and control groups

The statistical modeling test by adjusting the effect of gender, age, and BMI before the intervention showed that there was no significant statistical difference between the average body temperature, respiration rate, systolic blood pressure, diastolic blood pressure, chest pain, cough, headache and disease complications including neurological, cardiac and respiration (P>0.05). However, the statistical

modeling test by adjusting the effect of gender, age, and BMI before the intervention showed that the average heart rate in the intervention group is 1.91 higher than the control group (P = 0.02) and the effect of time is also significant (P<0.001) (figure 2)

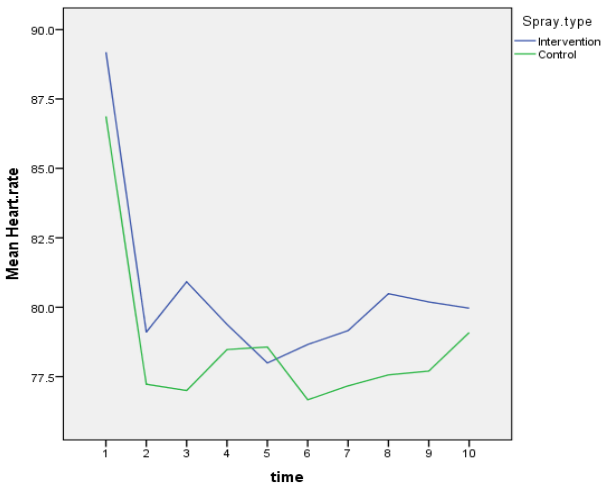



**Figure 2.** The effect of duration of using PHR-160 spray on average heart rate in two intervention and control groups

Also, the statistical modeling test showed that the difference in the average percentage of oxygen saturation in the intervention and control groups is not significant (P = 0.43), but the effect of time was statistically significant (P < 0.001) so that after each day the average percentage of saturation Oxygen increased by 0.3 units (figure 3).

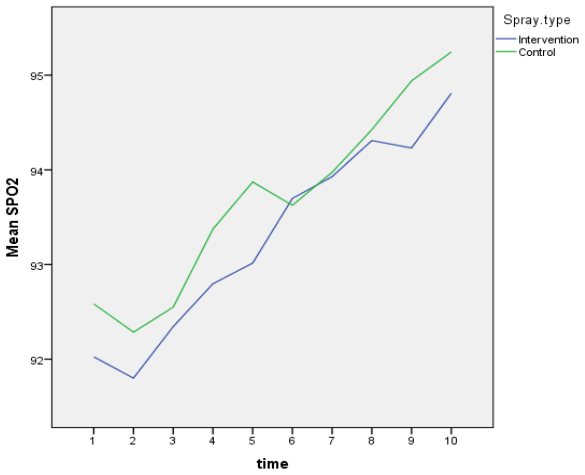



**Figure 3.** The effect of the duration of using PHR-160 spray on the average saturation percentage in two intervention and control groups

The results of the CT scan showed that the condition of 86% of the patients in the intervention group and 75% of the patients in the control group is improving. The percentage of recovery in patients in the intervention group was about 11% higher, but there was no statistically significant difference between the two groups (P = 0.06). After using PHR-160 spray for ten days, there was no significant difference in drug side effects (nerves and heart) in the intervention and control groups (P<0.05). However, the statistical modeling test showed that the intervention of the time effect is statistically significant (P<0.001) and the chance of respiratory complications in patients using the spray decreased by 0.09.

## Discussion

The results obtained from the use of PHR-160 spray in patients with Covid-19 showed that this spray could not relieve abdominal pain, anorexia, chest pain, cough, diarrhea, fatigue, headache, joint pain, taste & smell disorder, respiratory discomfort, shortness of breath, sore throat, nausea, and vomiting in patients, but it was effective in reducing muscle pains that most patients with Covid 19 suffer from [20, 21]. The effect of reduction in muscle pains can be originated from the active ingredient Menthol and Saffron in the spray used. The studies conducted on these substances show that they can be effective in reducing muscle pain when combined with other substances [22, 23]. In the study of Kanezaki et al [24] that were in contrast with our results, it showed that the Olfactory stimulation of L-menthol relieves shortness of breath in patients with COPD. Also, in another study conducted by Zilaee et al. on the effects of saffron on the clinical symptoms and severity of asthma in patients with mild and moderate persistent allergic asthma, the results showed that this substance can lead to a decrease in shortness of breath during the day and night, decreasing Asthma severity, reduction of systolic and diastolic blood pressure, reduction of triglyceride and low-density lipoprotein cholesterol and reduction of eosinophil and basophil concentration. The differences in the results of different studies can be influenced by the size of the sample, and the type and severity of the investigated diseases.

One of the problems of patients with covid-19 is shortness of breath caused by the accumulation of secretions and the presence of sticky mucus [21, 25]. In examining the effect of PHR-160 spray on this complication, the results were not statistically significant and indicate that this spray cannot lead to the reduction and relief of the symptoms related to shortness of breath, the occurrence of bronchitis, and its complications. Meanwhile, the results of this spray in the study of Roshandel et al showed that PHR-160 spray is safe and can be effective in improving the respiratory symptoms of patients with covid-19. The difference in the results of these studies, as mentioned in the limitations of Roshandel et al.'s study, can be due to the small number of samples examined and the short duration of the study (5 days) [26].

The results showed that the average heart rate in the intervention group is higher than the control group. In the conducted investigations, a study confirming the relationship between the effective ingredients used in PHR-160 spray with increased heart rate was not found, but it is important to note that the disease of Covid-19 may be caused by cytokine storm, hypoxic injury, Electrolyte abnormalities, plaque rupture, coronary spasm and direct damage to endothelial and myocardial lead to a wide range of complications and abnormalities in ECG [27].

The use of CT scans and the evaluation of lung involvement in patients with covid-19 is one of the criteria of clinical judgment to assess the condition of patients. The higher the percentage of lung involvement, the greater the deterioration of the disease. In this research, the results showed no significant difference in the CT scan results between intervention or control groups

## Conclusion

Based on the results of this research, it can be concluded that PHR-160 spray has no beneficial effects in controlling the symptoms of patients with covid-19 and cannot play a significant and effective role in improving the patient's condition and reducing the complications caused by the disease.

### Research Highlights

**What Is Already Known?**

Covid-19 is a disease that has become the concern of all health professionals around the world. Comprehensive efforts have been made to contain and control this disease, which has helped to some extent, but finding a definitive treatment is still an important and unfinished challenge that requires the efforts of a wide range of specialists around the world.

**What Does This Study Add?**

The PHR-160 spray, which is based on herbal medicine, could not be effective in improving and controlling the symptoms and complications of covid-19.

### Ethical Approval

This study is based on a research project approved by Ethics Committee of Baqiyatallah University of Medical Sciences with the code of ethics IR.BMSU.REC.1398.387. It was also registered at the Iranian Center for Clinical Trials (IRCT) with IRCT20200731048257N1 verification code. Informed consent was obtained from all individual participants included in the study.

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**Authors' Contributions**
All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

**Conflict of Interest**
None

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