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Investigation the effect of PHR 160 spray on the laboratory outcome of patients with covid-19 - a randomized clinical trial study- Supplementary outcome

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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 controlling and improving the laboratory results of patients with 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- The existence of concomitant diseases, and 3- Tests performed at the beginning of admission and from the first to the 10th day. The necessary sample volume was determined 330 people and informed consent was obtained from them to participate in the research. Data were analyzed using an independent t-test and chi-square test.

Results: There was no significant difference between the intervention and control groups in the study of demographic variables, examined diseases 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, patient mortality, laboratory tests and complications of the disease in the two groups (P>0.05).

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

Keywords: PHR-160 spray, Covid-19, laboratory results, patient, cineole, menthol, safran, safranal, and crocin

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Background

Covid-19 is a highly contagious respiratory disease caused by the SARS-CoV-2 virus. This disease can affect multiple organs and cause a wide range of symptoms[1]. Since its emergence in December 2019, to prevent the spread of Covid-19, public health measures such as wearing masks, social distancing and frequent hand washing have been recommended, as well as measures such as the use of vaccines and antiviral drugs to help prevent infection and the severity of the disease decreased. However, finding an effective and definitive treatment remains a challenge. Herbal treatments as a possible option can have a preventive or supportive role in patients with covid-19 [2, 3]. Researchers are facing another challenge in ensuring access to effective treatments for low-income areas. Eradicating Covid-19 is essential to provide a definitive solution to this global health crisis[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. The unique properties of each of the effective ingredients in traditional medicine, which are usually extracted in the form of essential oils, create

specific effects. For example, Cineole can reduce the severity of chronic obstructive pulmonary disease (COPD)[5], treat airway inflammation in bronchial asthma[6] and control the concentration of airway mucus by inhibiting cytokines[7]. Menthol is effective for the treatment of sore throat, cough related to colds or respiratory infections[8],nasal congestion caused by inflammation of the nasal mucosa[9] and mild asthma[10]. In in vivo studies, crocin has a protective effect on allergic asthma[11], Reduces inflammation of the respiratory tract[8] and a reduction in lipopolysaccharide-induced acute respiratory distress syndrome[12]. Safranal prevents lung inflammation[13], can relieve asthma[14] and has antitussive effects[15], anti-inflammatory[16], anti-human immunodeficiency virus(HIV) and anti-Herpes Simplex(HSV) effects[17]. In the covid-19 disease, extensive changes occur in the body. Among these changes, we can mention changes in the levels of laboratory items such as red blood cells(RBCs), hemoglobin(Hb), hematocrit(HCT), mean body volume(MCV), and C-reactive protein(CRP)[18]. Also, studies have shown that in patients with severe covid-19 disease, there is a significant increase in the number of white blood cells (WBC) and a decrease in the number of lymphocytes and platelets compared to milder disease[19]. Several studies have been conducted to find effective medicinal compounds in the treatment of Covid-19, and essential oils are among these medicines. As a secondary metabolite in medicinal plants, essential oils are a mixture of volatile oil compounds and have antimicrobial, anti-inflammatory, antioxidant and anti-cancer properties without causing adverse effects. These compounds have many uses in pharmaceutical and food industries. Therefore, the purpose of this study is to investigate the effectiveness of PHR-160 spray, which is a combination of effective ingredients, in the treatment of Covid-19.

Method

This article is the second part of a study with doi:10.30491/IJTMGH.2023.385549.1345 that was published in the International Journal of Travel Medicine and Global Health. 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 (Flowchart 1).

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 dementia, patients receiving immunomodulatory drugs, patients requiring hospitalization in the intensive care unit, patients with uncontrolled heart, kidney, or liver failure, and pregnant or breastfeeding women.

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- The existence of concomitant diseases, and 3- Tests performed 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[20].

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 of all variables (patient characteristics including demographic information) before the start of the intervention (baseline) two groups were compared. Considering that the approach of this study is superior, therefore the percentage of need to receive special care 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 was 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:

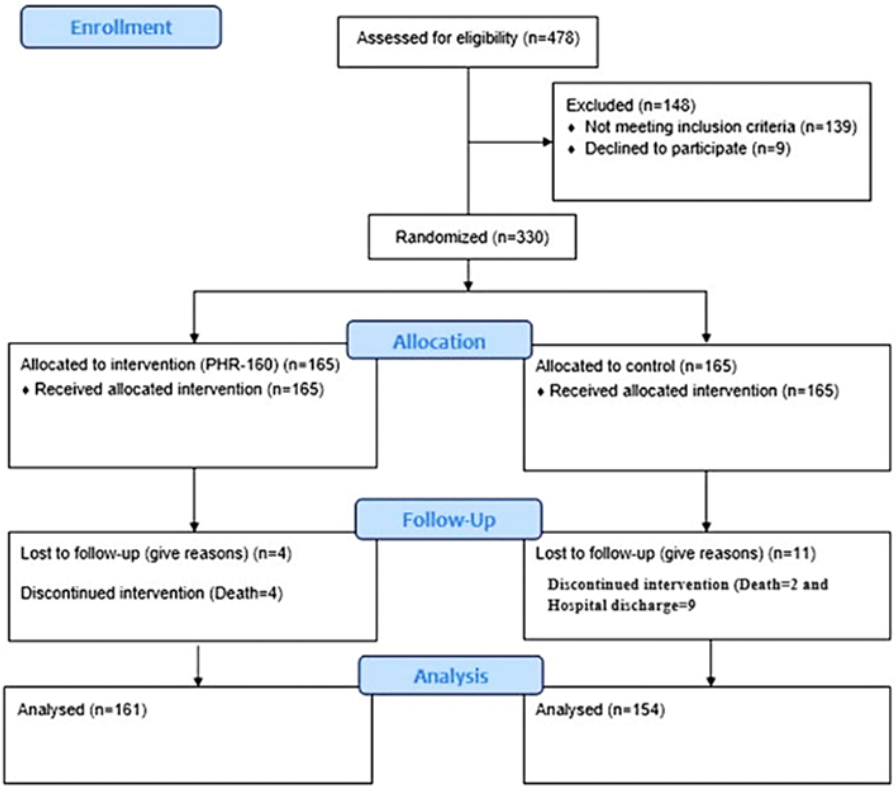
1- A lung and infectious disease specialist and clinical pharmacist with sufficient experience in the treatment of Covid-19
2- An epidemiologist with sufficient experience in the methodology of clinical trial studies
3- A statistician

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

Patients were given the right to choose and informed consent was obtained from them 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 people were in the control group, and the average age of the people participating in the study was 51.37 ± 13.72. Other demographic characteristics are shown in Table 1.

Table 1: 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

In the study of demographic variables before using PHR-160 spray, there was no significant difference in the intervention and control groups (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 the mortality of patients in the two intervention and control groups (P>0.05). 16.8% of the patients in the intervention group and 24% of the patients in the control group had blood pressure, but this difference was not significant (P>0.05). Also, 2.5% of patients in the intervention group and 1.3% of patients in the control group had heart disease, and this difference was not statistically significant (P>0.05). Other examined diseases are listed in Table 2.

Table 2. Comparison of examined diseases in two intervention and control groups

Variable \ Group	Intervention Abundance(percentage)		Control Abundance(percentage)		p-value
	No	Yes	No	Yes	
High blood pressure	134(83.2)	27(16.8)	117(76)	37(24)	0.11
Heart disease	157(97.5)	4(2.5)	152(98.7)	2(1.3)	0.68
Chronic lung disease except for asthma	160(99.4)	1(0.6)	153(94.4)	1(0.6)	0.99
Chronic renal disease	158(98.1)	3(1.9)	151(98.1)	3(1.9)	0.99
Mild liver disease	157(97.5)	4(2.5)	147(95.5)	7(4.5)	0.31
Moderate to severe liver disease	161(100)	0(0)	152(98.7)	2(1.3)	0.23
Hypothyroidism	151(93.8)	10(6.2)	144(93.5)	10(6.5)	0.91
Chronic neurological disease	151(98.1)	3(1.9)	151(98.1)	3(1.9)	0.99
diabetes	297(92.24)	25(7.46)	282(91.56)	26(8.44)	0.52
Chronic blood disease	161(100)	0(0)	153(99.4)	1(0.6)	0.49
Rheumatoid Arthritis	161(100)	0(0)	151(98.7)	2(0.6)	0.23
Hyperlipidemia	161(100)	0(0)	153(99.4)	1(0.6)	0.49

After using PHR-160 spray for 10 days, there was no significant difference in the complications of the disease (anaphylaxis, gastrointestinal, eye, gland, blood, skin, and kidney) in the intervention and control groups (P>0.05). Also, the statistical modeling test by adjusting the effect of gender, age, and BMI before the intervention showed that there is no statistically significant difference in the complications of the disease (anaphylaxis, gastrointestinal, eye, gland, blood, skin, and kidney) in the two intervention and control groups and the effect of time was also not significant (P>0.05).The statistical modeling test by adjusting the effect of gender, age, and BMI before the intervention showed that there wasn't a significant statistical difference between the mean RBC, WBC, Hb, ALKPH, K, FBS, BUN and Cr in the intervention and control groups and the effect of time was not significant (P>0.05). But the mean number of white blood cells increased over time in both groups (P < 0.001).After using PHR-160 spray for ten days, in the tests of the number of red blood cells (RBC), the number of white blood cells (WBC), hemoglobin (Hb), aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALKPH), sodium (Na), potassium(K), C-reactive protein (CRP), fasting blood sugar (FBS), blood urea nitrogen (BUN), and creatinine (Cr) there were no significant differences in the intervention and control groups(P>0.05).The statistical modeling test by adjusting the effect of gender, age, and BMI before the intervention shows that the average platelet in the intervention group is significantly lower than the control group by 0.23 (P<0.05) and the effect of time is also significant (P<0.001) (figure 1).

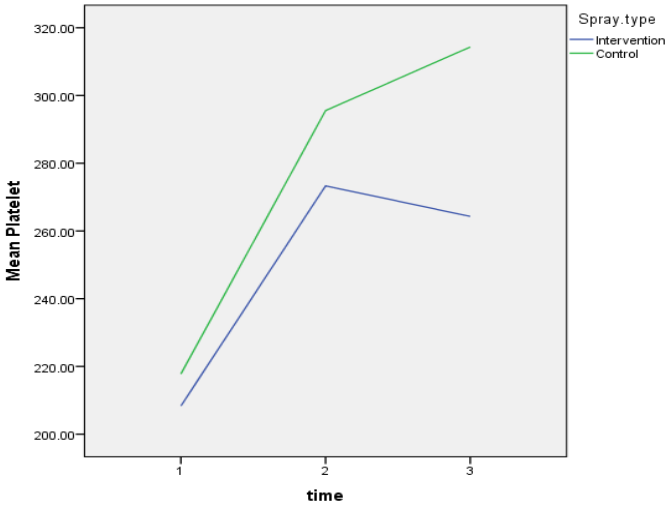


Figure 1. The effect of duration of using PHR-160 spray on mean platelet in two intervention and control groups.

Also, the statistical modeling test by adjusting the effects of gender, age, and BMI before the intervention showed that although the average CRP in the intervention group was 1.71 times lower than the control group, there was no statistically significant difference between the two groups(P>0.05) but the effect of time was significant and the average CRP in both groups decreased significantly over time (P<0.001). (figure 2).

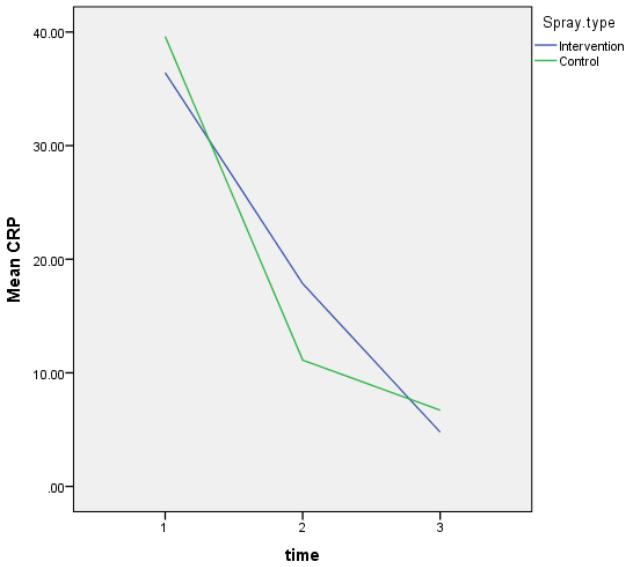


Figure 2. The effect of duration of using PHR-160 spray on mean CRP in two intervention and control groups

Discussion

The results of the research showed that there is no significant difference in the presence of co-morbidities in the two intervention and control groups, but the high blood pressure disease is in line with the results of the studies of Nasralehzadeh et al [21] and Arab et al [22] accounted for the highest percentage of concomitant diseases. The presence of co-morbidities has always been one of the concerns related to the recovery process of the covid disease and the results of the studies have also shown that most of the covid-19 patients had underlying diseases such as high blood pressure, diabetes mellitus and cardiovascular disorders, as well as the accompanying Diseases with covid-19 have led to an increase in mortality in these patients [23-25].

The results of liver tests and CRP in both intervention and control groups were high, consistent with other studies[26-28]. But the effect of time has an effect on these tests and the average of liver tests including ALT and AST and the average of CRP in both groups decreased significantly over time. Also, the average ALT, average AST and average CRP in the intervention group were 2.93, 2.46 and 1.71 units lower than the control group.

Saffron contains three main compounds including crocetin esters, picrocrocin and safranal, whose strong

antioxidant and anti-inflammatory effects have been investigated and confirmed in some cases in some diseases such as Alzheimer's, cancer and depression. In a review study by Alexios-Fotios A Mentis et al., which reviewed in vitro and in silico studies, it states that it seems that saffron essential oils and its other compounds have immune system modulating and anti-asthmatic effects. In addition, it seems that crocin can reduce the cytokine cascade associated with covid-19 and the expression of the angiotensin-converting enzyme 2 (ACE2) gene [29]. Also, crocin, which is one of the effective ingredients used in PHR-160 spray, has platelet anti-apoptotic properties[30]. but in this study, the patients who used the spray had a significantly lower mean platelet count. Of course, the occurrence of thrombocytopenia and thromboembolic complications have always been of concern in patients with covid-19 [31, 32], which seems not to be affected by crocin to prevent this complication.

In a study on rats, Mowafy et al investigated the protective effect of crocin against copper oxide nanoparticles and the results showed that crocin has a protective effect against copper oxide nanoparticles[33]. Also, contrary to the results of our study, in the study of Zuiming Jiang et al[34], crocin leads to a decrease in alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), urea nitrogen. Blood (BUN), creatinine, bilirubin, albumin, and total protein.

Haji Beigi et al used a diet based on traditional Iranian medicine containing saffron to treat patients with Covid-19, and the results showed that it can be effective in reducing inflammatory markers such as CRP. However, unlike the results of this study, our study showed that the use of PHR-160 spray in the intervention and control groups did not have a significant difference in reducing CRP. The difference in the obtained results can be caused by the difference in the method of using effective substances in the two studies[35].

In addition, the review study by Amjad M Husaini et al states that saffron has been able to play an important role as a food or drug supplement by using anti-inflammatory and antioxidant effects in reducing the severity of symptoms related to patients with Covid-19 [36].

Eucalyptol, also known as 1,8-cineole, is a potential inhibitor for COVID-19 (main protease-Mpro) with effective antiviral properties, but is subject to physical and chemical instability and poor water solubility. Alaa S. Tulbah et al used this substance in the form of nebulized eucalyptol nano-emulsion (EUC-NE) in their study and confirmed the antiviral activity of EUC-NE formulation against Covid-19 [37]. However, in our study, no results were found to improve the results of laboratory parameters in patients with covid-19 following the use of this substance.

Limitation

In the method of using the spray, the patients were advised to use the spray at the rate of 10 puffs per day. However, due to the high number of patients, it was not possible to follow-up using 10 times a day by the researchers.

Conclusion

Based on the results of this research, it can be concluded that PHR-160 spray has no beneficial effects in controlling and improving the laboratory results 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 laboratory results and complications of covid-19.

Conflict of Interest

None

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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Baqiyatallah University of Medical Sciences, Tehran, Iran

Authors' Contributions

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

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