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Original Research

The Efficacy of a Persian Medicine-Based Dietary Protocol on Hospitalized COVID-19 Patients: A Randomized Controlled Trial

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Abstract

This study aimed to evaluate the effectiveness of a Persian Medicine-based dietary protocol (PM diet) in patients infected with COVID-19. A randomized clinical trial was performed from July 2020 to January 2021 in Tehran, Iran. Eighty patients admitted due to pulmonary dysfunction caused by COVID-19 were randomly allocated into two groups: the PM diet or the common hospital (CH) diet. Eight beds in 2 rooms were considered for each group. Patients were randomly hospitalized in these rooms and received these diets up to discharge or death.. Oxygen saturation level and duration of hospitalization, the rate of mortality, duration of fever, and duration of cough were considered as the primary and secondary outcomes, respectively. Oxygen saturation and fever duration were not different between groups (P value= 0.08, 0.312, respectively). But the duration of hospitalization and the duration of cough in the PM diet group were significantly shorter than in the CH diet (P value= 0.002, 0.009, and HR=2.02, 1.86 respectively). The mortality rate was significantly lower in the PM diet group than in the CH diet group (Odds ratio: 0.12, P value=0.026). PM diet caused a lower mortality rate, shorter hospital stay, and better improvement in cough, but did not have a significant effect on O_2 saturation and fever.

Keywords: COVID-19; Diet; Persian medicine; Nutrition; Complementary therapies

Introduction

In January 2020, the COVID-19 was declared a pandemic by the World Health Organization (WHO). COVID-19 was first reported in Wuhan Province, China. The virus is a member of the beta-coronavirus family and is genetically very similar to the SARS virus [1]. COVID-19 present with clinical signs including fever, dry cough, weakness, lethargy, reduces appetite, nausea, and vomiting [2]. Most COVID-19 patients develop mild respiratory illnesses that can be cured without special treatment [3]. But it also may cause severe respiratory inflammation that leads to death in some cases. Moreover, it is indicated that about 9.1 % of COVID-19 cases older than 60 years need hospital admission [4]. Despite researches, there is currently no conclusive treatment for COVID-19 in conventional medicine. Using the capacity of traditional medicines can be considered helpful in this

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situation [5]. For instance, some studies confirmed the efficacy and safety of Chinese Medicine in clinical cures and decrease death in COVID-19 patients [6].
Persian Medicine (PM) as one of the oldest paradigms of traditional medicine has been established based on a holistic viewpoint of the human body and a personalized manner, for managing patients [1]. In this viewpoint, the use of food for treatment is preferred rather than the use of medicines, because the foods are usually more compatible and cause fewer side effects. There are a lot of dietary recommendations in PM for different kinds of diseases and recent studies confirmed their effectiveness in some diseases such as cirrhosis [7]. Although COVID-19 is an emerging disease and there is no specific diet for it in PM, by reviewing PM references, many foodstuffs are found that have been prescribed for treatment of such fever, infections, and respiratory dysfunction as the main figures of COVID-19 [8,9].
The effectiveness of many herbal and traditional medicines for improving the symptoms and complications of the disease has been revealed in several studies [10]. There has always been concern about their use in these patients, especially hospitalized patients who also receive different types of common medicines, due to the possibility of interactions [11,12].
The attention to functional foods and nutraceuticals have also an increasing trend in prevention and treatment of diseases in the last decades and highlight the necessity of the nutriotional management instead of complicated formulation medicines [13]. However, it seems no study has been conducted for evaluating a dietary plan in the treatment of COVID-19 patients. Considering all these facts, this study aims to evaluate the effectiveness of a dietary plan based on PM recommendations for hospitalized patients due to COVID-19.

Materials and Methods

Study design
This study was performed as a randomized clinical trial from July 2020 to January 2021 in Tehran, Iran. It was approved by the ethics committee of Babol University of Medical Sciences and was registered in the IRCT with the code IRCT20200105046009N4. Written informed consent was given from all participants.

Participants
In this study, patients admitted to the Sevom-e-Shaban Hospital, Damavand, Tehran, Iran, for the probable pulmonary infection with COVID-19 were randomly entered into the study.

Inclusion criteria
Patients aged 18 to 75 years with moderate and severe COVID-19 pneumonia based on WHO classification who had clinical signs and symptoms (fever, cough, dyspnea, O_2 saturation ≤ 94%) and had positive RT-PCR or infiltration in Chest X-Ray were included in the study [14].

Exclusion criteria
The patients with any chronic uncontrolled cardiac, renal, metabolic, etc. diseases, the patient with intubation, and who had nausea and vomiting and oral intolerance were excluded. Treatment-resistant hypoxemia, decreased level of consciousness and hemodynamic instability were other exclusion criteria.

Randomization
Cluster Randomization was used in this study. The patients' hospital rooms were considered clusters. In the hospital, 16 beds in 4 rooms (4 beds in each room) were allocated for the study. In the hospital, 2 rooms (8 beds) were randomly assigned to the PM diet and 2 rooms (8 beds) to the standard diet as the control group. The selection and assignment of rooms to the diet were random using a random digit table.

Entering the study
Patients after clinical and paraclinical diagnosis based on inclusion criteria entered the study. Baseline data including age, gender, marital status, weight, type of occupation, addiction status, and other medical history was recorded on the first day.

Primary outcome
O_2 Saturation rate (percent) was considered the primary outcome that was recorded at least once a day that was recorded every morning without oxygen therapy.

Secondary outcome
Duration of hospitalization, the rate of mortality, duration of fever, and duration of cough were the secondary outcomes.

Sample size
The sample size was calculated by G*Power 3.1.9.2 software. To compare O2 saturation changes in the two groups for 4 repetitions, with the effect size of 0.2, the first type error of 0.05, and power 80% the minimum required sample size in each group was calculated for 36 patients. With the probable 10% of loss during the study, the final sample size was 40 patients in each group.

Intervention
The collection of selected medicinal plants which are usually known as functional foods from PM books for this dietary plan and the evidence related to their new studies have been published in a previous review study [15].

Based on that research, a hospital diet for COVID-19, as an evidence-based protocol of a clinical trial was proposed [15]. This Persian Medicine-based diet (PM diet) was used for the intervention group of COVID-19 patients. A "Tonic Lung Soup (TLS)" was introduced in this diet to use every day with this recipe: A cup of wheat semolina cooked well with 5 to 6 glasses of water, a medium carrot with a clove of garlic, and a small onion. It was possible to add some noodles (vermicelli) and a tablespoon of dried nettle leaves to the soup. Then in the last twenty minutes, a tablespoon of chopped parsley and dill, 25 grams of butter or a tablespoon of sesame oil, and a balanced amount of salt and turmeric were added. To change its taste, on some days a small amount of fresh lemon juice or half a lemon was added. Meat and chicken were not used in this diet [15].

Control groups received routine Common Hospital diet (CH diet) in Iran. The diet continued up to discharge or death. Patients who became ventilated during the study received their diet by gavage.

Other necessary medicines and treatment methods including Remdesivir, Tocilizumab (Actemra), Enoxaparin, Heparin, Famotidine, Naproxen, Dexamethasone and Meropenem were prescribed in both groups based on flowchart of diagnosis and treatment of COVID-19 which was published by ministry of health and education of Iran during that time without considering the grouping of diet.

Data analysis

Descriptive analysis was performed as mean (±standard deviation) for quantitative variables and frequency (percentage) for qualitative variables. To compare the parameters at baseline, we used independent samples t-test and chi-square test. Also to evaluate the effectiveness of the PM diet on primary and secondary outcomes we used repeated measure analysis, generalized estimating equations (GEE) and, survival analysis (Cox regression, Kaplan-miere, and Log-rank test). P values less than 0.05 were considered significant.

Results

Out of 89 patients who were assessed for eligibility criteria, 80 patients based on inclusion criteria entered the study. As they were hospitalized, all of them were in access up to the end of the study. The flowchart of the study is shown in figure1. The mean age of patients was 56.99 ± 16.67 (min = 19, max = 92). Forty-six (57.5%) were male and 34 (42.5%) were female. Seventy-eight of them were married and 2 were single. The baseline data were not different between groups. The details are shown in table 1.

Primary outcome

O_2 Saturation rates in baselines were 81.49±9.9 in the PM diet and 83.6±8.2 in the CH diet (P value=0.08). O2 Saturation rate improved in both groups during hospitalization (P value <0.001 in both groups), but no significant difference was seen between groups of the PM and CH diet (P value=0.272).

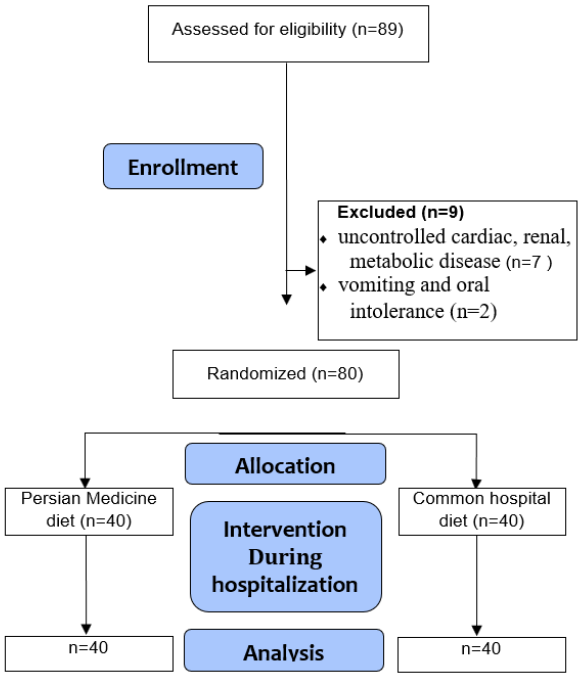

Figure 1. Flowchart of the study

Secondary outcomes

The duration of hospitalization was 6.3±0.4 (median=6) days in the PM diet which was significantly shorter than the CH diet with 10.1±1.4 (median=8) days of hospitalization (Hazard ratio-HR=2.02, P value= 0.002). The number of deaths was 7 patients in the CH diet group which was significantly higher than the PM diet group with 1 death (P value=0.026, Risk ratio=3.73, Risk difference=15%, NNT=6.66). The details are shown in figure 2.

The duration of cough during hospitalization in the PM diet group was 3.9±0.2 days (median=4 days) that was significantly shorter than the CH diet group with 4.97±0.4 days (median=5 days) (HR=1.86, P value= 0.009).

The fever duration in the PM diet group was 2.09±0.16 days (median=2 days) after hospitalization that was not significantly different from the CH diet group with 1.7±0.14 days (median=2 days) (HR=1.04, P value=0.312).

The fever duration in the PM diet group was 2.09±0.16 days (median=2 days) after hospitalization that was not significantly (Log-rank P value=0.312) different from the CH diet group with 1.7±0.14 days (median=2 days).

Table1. Demographic data of two groups of Persian Medicine diet and Common Hospital Diet

Demographic data		Persian Medicine diet group (n = 40)	Common Hospital diet (n = 40)	P value
Sex (female), n(%)		18 (45%)	16 (40%)	0.503
Age, year , Mean(±SD)		54.56(±17.25)	59.41(±15.90)	0.189
Height (cm), Mean(±SD)		173.51(±5.61)	173.73(±5.79)	0.862
Weight (Kg), Mean(±SD)		77.73(±9.83)	76.15(±9.55)	0.461
BMI , Mean(±SD)		25.82(±3.14)	25.22(±2.96)	0.372
Marital status (married), n(%)		39(97.5%)	39(97.5%)	1
Underlying disease	Diabetes, n(%)	0 (0)	6 (15%)	0.07
	Heart disease, n(%)	7 (17.5%)	5 (12.5%)	
	Renal disease, n(%)	0 (0)	1 (2.5%)	
	Lung disease, n(%)	6 (15%)	5 (12.5%)	
	Not, n(%)	27 (67.5%)	23 (57.5%)	
Smoking, n(%)		4 (10%)	9 (22.5%)	0.131
Addiction, n(%)		3 (7.5%)	5 (12.5%)	0.457

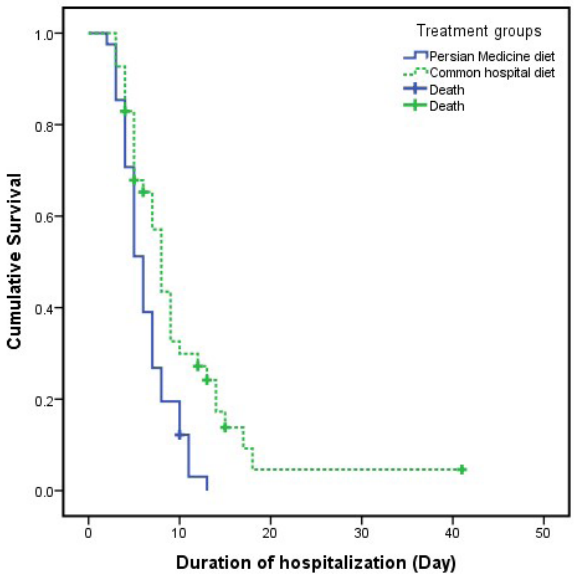

Figure 2. Duration of hospitalization and rate of mortality between two groups of Persian Medicine diet and Common hospital diet

Discussion

In this randomized clinical trial study, the proposed PM diet caused a significant decrease in duration of hospital stay, duration of cough, and also mortality rate compared with the CH diet without any significant effect on O_2 saturation. In the case of treatment, the probability of improvement increases by 15%. In other words, 7 persons are needed to be treated to prevent one additional death.

It seems that this study is the first study that evaluated a dietary plan based on traditional medicines on COVID-19 outcomes. However, the efficacy of traditional medicines for the prevention and treatment of COVID-19 disease has been discussed in some studies. A systematic review and meta-analysis study which included a total of 25 RCTs involving 2222 participants showed that Traditional Chinese Medicine plus conventional treatment was significantly more efficient than conventional treatment alone in clinical cure and chest image improvement and could reduce clinical deterioration, and mechanical ventilation or death rate [6]. Some other clinical studies regarding the use of traditional medicine for the treatment of COVID-19 showed that the use of traditional medicines along with drug therapy can reduce the mortality rate of these patients [15].

Moreover, the results of a study by Karimi et al. showed that using herbal medicines extracted from PM books in the forms of capsule and decoction in hospitalized COVID-19 patients could significantly decrease the duration of hospital dyspnea, accelerate clinical improvement, and decrease some symptoms in the treatment group compared with the standard care group [16]. This study revealed that using the recommendations of PM to treat COVID-19 disease can be useful. Decreases in hospital stay and cough duration were common results between Karimi et al. study and our study. But in the case of O_2 saturation improvement, significant difference was found between the two groups in the Karimi study in contrast to our study.

Another clinical trial by Setayesh et al. showed the administration of capsules containing *Glycyrrhiza glabra, Punica granatum*, and *Rheum palmatum*, and the second capsule of *Nigella sativa* powder resulted in a reduction of hospitalization duration, similar to our

results and improvement of O_2 saturation in contrast to our results [17].

In addition, there are some studies that have evaluated various PM dietary plans in other diseases. Such as a study by Ehsani et al. which compared the PM diet and current diet on patients with cirrhosis. Results showed a significant decrease in alanine aminotransferase and resolution of icterus in the PM diet group [7]. Despite publishing some guidelines about nutritional issue in hospitalized COVID-19 patients [17] and some studies which indicated the association between types of usual diet and the probability of moderate to severe COVID-19 in the population [7,18], it seems no clinical trial has been published in terms of evaluating effects of a certain dietary in COVID-19 patients yet and our study may be the first one. But the role of dietary changes was studied in some other respiratory diseases. Calder et al. evaluated the role of 12-week diet consisting of high doses of omega-3 fatty acids, vitamin D, and high-quality protein with a good safety profile in moderate-to-severe Chronic Obstructive Pulmonary Disease (COPD) patients. Also, a decrease in dyspnea was reported [19]. Results of a systematic review and meta-analysis showed diet counseling with or without oral nutrition supplementation, in comparison to standard care, did not reduce inpatient rates of 30-day mortality and the hospital stay duration in malnourished or at risk of malnutrition patients [20]. The notable point is that it seems most studies about diet effectiveness are conducted on chronic diseases and our study is among unique researches on acute situations.

In this PM-based diet, some important PM principles of nutrition were implemented. For instance, decreasing or eliminating the consumption of red meat during acute illnesses and also eliminating some foods that produce bloating or slow-digesting foods such as beans can be mentioned.

Along with that, considering principles of new nutrition science and evidence about the role of deficiencies in protein energy, trace elements like zinc, copper, selenium, and iron and specific vitamins like A, B6, B12, folate, C, D, and E in increasing susceptibility to respiratory infections, all essential types of nutrients were included in this plan [21,22].

The most important part of the diet was TLS soup which contained wheat, carrot, garlic, onion, dill, parsley, nettle, butter or sesame oil, turmeric, and lemon juice. The other important ingredients of this diet were apple, quince, pomegranate juice, honey, sweet orange, saffron, and rose water. All these foodstuffs have antiviral, antioxidant, and analgesic properties and have sufficient evidence of effectiveness for infectious, respiratory, and inflammatory diseases [15]. For example, wheat has several components including dietary fiber, resistant starch, phenolic acids, alkylresorcinols, lignans and tocols which could improve the immune system through antimicrobial properties, antioxidant effects, vitamin E activity and induction of immune responses [23].

Some studies showed that natural extract from carrot (*Daucus carota* L.) accelerated innate immune and antiviral responses, and reduced symptoms of an acute respiratory viral infection [24,25]. It was also shown carrot pomace polysaccharide can activate dendritic cells and increase influenza vaccine efficacy [26].

Garlic (*Allium sativum* L.) as a permanent part of the diet plays an important role in the prevention and treatment of infections and inflammations [27]. The presence of sulfur-containing phytochemicals in garlic provides substantial immunomodulatory, anti-inflammatory, and cardioprotective features. The antiviral potential of garlic was documented against a number of viruses like influenza B, HIV, herpes simplex virus and coxsackievirus species. In an *in silico* approach to the inhibitory effect of garlic against SARS-CoV-2, some specific sulfur-containing phytochemicals were considered as possible constitutes to inhibit the Mopro, the main protease of SARS-CoV-2, through H-bonds with this protease. Moreover, the concentration of 0.1 mL of garlic clove extract revealed a potent *in vivo* inhibitory effect against SARS-CoV-1 multiplication, probably due to the formation blocking of structural proteins and genetic materials [28].

Turmeric (*Curcuma longa* L.) as another permanent part also has strong evidence of effectiveness as a good source of anti-inflammatory agents. Curcumin, the main component of turmeric, completely neutralized SARS-CoV-2 *in vitro* [29]. It exhibited good ability to inhibit influenza A virus induced lung tissue injury by blocking nuclear factor κB signaling and inhibiting the production of inflammatory cytokines. Curcumin is a natural ligand of peroxisome proliferator-activated receptor-γ, which represses the inflammatory process by reducing cytokine production [30].

Nettle (*Urtica dioica* L.) has shown the ability to inhibit severe acute respiratory syndrome coronavirus replication in a lethal SARS-CoV BALB/c mouse model [31]. Moreover, this plant has the potential to inhibit viral spike protein [32].

Sesame (*Sesamum indicum* L.) and its oil are well-known foodstuffs for immune system improvement. They also possess significant antioxidant and anti-inflammatory effects [33]. In addition, *in silico* studies suggested that sesame lignans could be an alternative source for the development of new natural medicines against COVID-19 [34].

Citrus spp. including lemon and orange as an important source of vitamin C, also is known as good immunomodulator substances. The antiviral property of hesperidin, main flavonoid of *Citrus* spp., was demonstrated using several computational methods [35].

Pomegranate (*Punica granatum* L.) juice is also usually a well-known nutraceutical food with an anti-inflammatory effect and has been introduced as a potential treatment for COVID-19 [36]. Urolithin was introduced as its effective agent against COVID-19 protease [37].

Saffron (*Crocus sativus* L.) and its main compounds, i.e., crocetin esters, picrocrocin, and safranal, present strong antioxidant, and anti-inflammatory action but have also been studied in COVID-19. Both *in vitro* and *in silico* studies showed saffron essential oils and other constituents have immunomodulatory and anti-asthmatic actions. Moreover, crocin appears to reduce the COVID-19-related cytokine cascade and downregulate angiotensin-converting enzyme 2 (ACE2) gene expression. Saffron's astragalin and crocin possess the potential to inhibit SARS-CoV-2 protease and spike protein, respectively [38].

Honey is also introduced as an important immunomodulatory and antiviral nutraceutical and its ingredients such as Camelyn have an inhibitory effect against SARS-CoV-2 [39].

It seems that a low-calorie and low-meat diet, based on the principles of PM, can reduce hospital stays and mortality rates in the PM group. The details of this diet were discussed in the protocol of the study [15].

In this study, no individuals were excluded from routine management. Patients were enrolled based on hospital rooms.

Our study has some strengths and limitations. The food materials used in this study were of high quality and have been purchased from the same centers, for example, bread with bran was obtained from a bakery, and honey from the most reliable store in Damavand city. Also this study was the first evaluation of this diet, patients with any kind of uncontrolled underlying diseases were excluded. Patients with nausea and vomiting also were excluded. In this study, the follow-up of the patients after discharge was not done, so it is suggested to pay attention to the follow-up of the patients in future studies.

Conclusion

According to the results of this study, PM low-red meat diet which included a certain soup and specific vegetables, fruits and additives could lower mortality rate, shorten hospital stay, and improve cough, but did not have a significant effect on O_2 saturation and fever. More studies with a larger sample size are recommended.

Conflict of Interests

There are no conflicts of interest.

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