Original Article

The Efficacy of Medium-Chain Triglyceride on the Prognosis and Outcome of Suspected COVID-19 Outpatients: A Randomized Controlled Trial

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Abstract

Background: The novel coronavirus disease (COVID-19), as a global concern, has affected different economic and social aspects, as well as health costs in various communities. Finding effective and available treatment is an urgent need. A recent study has demonstrated that the ketogenic diet (KD) activates innate immunity and has a protective property against virus infection. Accordingly, we conducted this study to find the effect of oral medium-chain triglyceride (MCT) on COVID-19 and its clinical manifestations.

Methods: This was a randomized clinical trial on 195 patients clinically suspected of COVID-19 referred to infectious disease clinics of Kerman. Patients were randomly assigned into two groups. The Control group received standard supportive treatment, the recommendation for carbohydrate avoiding and diet modification. Patients in the intervention group received all mentioned recommendations beside MCT oil. Patients` clinical symptoms, including body temperature, respiratory rate, body pain, and dyspnea, were recorded in a checklist and analyzed.

Results: The mean age of patients was 37.78 ± 12.42 years in the intervention group and 40.81 ± 13.23 years in controls ($P = 0.231$). The patients in the intervention group had lower duration of weakness ($P = 0.004$), body pain ($P = 0.004$), dyspnea ($P = 0.004$), gastrointestinal manifestations ($P < 0.001$), sore throat ($P < 0.001$), increased respiratory rate ($P < 0.001$), and high intensity of cough ($P = 0.002$). Indeed, weakness, cough frequency, sore throat, and gastrointestinal complications were significantly lower in the females of the intervention group ($P = 0.006$, $P = 0.030$, $P = 0.005$, and $P = 0.001$, respectively). In contrast, in the males of the intervention group, manifestations such as respiratory rates, dyspnea, cough intensity, and sore throat were significantly lower than those in the control group.

Conclusion: Administration of MCT in outpatients suspected of COVID-19 alleviated clinical symptoms such as increased respiratory rate, cough intensity, dyspnea, body pain, and gastrointestinal symptoms and helps them overcome the probable disease morbidity.

Keywords: Medium-chain triglyceride oil, COVID-19, Pneumonia, Dyspnea, Iranian traditional medicine

Introduction

The 2019 novel coronavirus disease (COVID-19), as a global concern, has terribly affected different aspects of the worldwide population. The outbreak of this disease was reported in Wuhan, China in late December 2019, then spread quickly throughout China and afterward in different parts of the world (1,2). The World Health Organization (WHO) called this widespread epidemic a pandemic on March 12, 2020. COVID-19 has imposed substantial economic, social, and health costs on various

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communities (3). According to a recent study, 80% of patients developed mild disease, and the mortality rate ranges from 2.3% to 14.8%, depending on the age of the patients (4). Accordingly, finding effective and available treatment is an urgent need. So far, many studies have been or are being conducted to assay different capacities of medicine (chemical drugs, herbal medicines, and non-pharmaceutical therapies) to find a way to alleviate this disease and its complications (5). Among various methods proposed to treat the disease, applying natural-based remedies that are usual in many people's daily diet is a notable strategy (6).

Triglycerides are classified based on their carbon number in three groups, including long-chain triglyceride (LCT), medium-chain triglyceride (MCT) with 6–12 carbons, and short-chain triglyceride (SCT) and they have different metabolisms (7). Coconut oil is a rich source of MCTs and modulates immune function (8). Unlike LCT, MCT is very ketogenic, and its oral administration might induce hyperketonemia in human beings (9).

Ketone bodies are a valuable source of energy and enhance the immune system. They could modulate inflammatory reactions and immunity in different pathways (10). Several diets have been described to take advantage of ketones. A ketogenic diet (KD) is a high fat, low carbohydrate diet which helps control some diseases such as seizures (11). A recent study has demonstrated that the KD activated innate immunity and has a protective property against influenza virus infection (10). MCT ketogenic therapy is a variant of KD in which there are no strict restrictions of classic KD regarding taking carbohydrates (12).

Considering the benefits of ketones and KD on the immune system and infections, the use of MCT and the inflammatory system of the human body, this study was designed with the aim of investigating the effect of oral MCT on COVID-19 disease and its clinical manifestation.

Methods
Design and population
The present study was a randomized clinical trial based on the Consort checklist, which was conducted on 195 suspected COVID-19 patients referred to specialized referral clinics of Kerman University of Medical Sciences in Kerman city, Iran from April 2020 to June 2021. Suspected COVID-19 patients between the ages of 18 and 65 with mild to moderate levels of involvement that according to the instructions of the Ministry of Health of the Islamic Republic of Iran were candidates for outpatient treatment were selected by a physician trained in the treatment of covid. Patients with a positive history of MCT oil allergy, drug allergy or asthma, pregnancy or lactation, congestive heart failure (CHF) or history of chronic renal failure (CRF), history of immunodeficiency, or recent glucocorticoid use were excluded from the

study. Also, patients with severe disease and respiratory distress were not included in the study.

Using the Random Allocation Software version 01 – (computer-based program with simple randomization), patients were randomly assigned into the two groups to receive either standard supportive treatment to alleviate symptoms (in accordance to the Ministry of Health guidelines) and prevention of sugar and starch consumption in the control group or all mentioned recommendations plus MCT oil in the intervention group.

Intervention
Since nutritional recommendations are of particular importance, we asked the participants of both groups to observe the following recommendations during 14 days:

- Eat food when there is a sincere appetite (at this time, the previous meal has been completely digested)
- Stop eating before you are full (food needs more space to digest).
- Take small bites (the bites should be small to be chewed well. Chewing food prevents indigestion, flatulence, constipation).
- Avoid overeating (overeating reduces the ability of the stomach to digest food)(13,14).
- Have a 15-minute light walking after each meal.
- Do not use anything between main meals and chew well.
- Avoid eating foods containing sugar.

Half of the patients received these diet recommendations and attitudes as the control group.

Patients in the intervention group received MCT oil from the beginning of the study plus the mentioned recommendations. Oral MCT oil (manufactured in NUTRICA Company, United Kingdom) was firstly administered half of the teaspoon in each meal and advanced to 2 teaspoons in the following days. In patients who developed gastrointestinal symptoms like diarrhea, abdominal pain, or distension, the amount of MCT was not increased and stayed at a steady dose.

MCT is obtained from virgin coconut oil. Virgin coconut oil is an edible oil obtained from the extract of fresh coconut kernel (*Cocos nucifera* L.), and it is used in baking sweets, bread and baby foods. MCT is used as a health supplement due to its content of medium chain fatty acids, which is used as an anti-obesity treatment and in the treatment of several minor diseases such as diarrhea, skin inflammations and injuries. Pure coconut oil is considered GRAS (generally recognized as safe) by the US FDA (2020) (15).

The MCT used in the present study (based on the specifications listed on the drug bottle by the manufacturer) consisted of caprylic (C8), capric (C10), and lauric (C12) fatty acids that are released by lipase enzyme after eating. The antiviral activity of pure coconut

oil is attributed to lauric acid and monolaurin, which causes the rash to be covered (16).

Demographic data (height, weight, body mass index, and waist circumference) were collected using a checklist. Traditional medicine recommendations about eating and drinking were given to all participants. Also, patients` clinical symptoms such as body temperature, the respiratory rate in one minute, weakness, body pain, severity and frequency of cough, dyspnea (any difficulty in respiration), sense of olfactory (unable to smell), sore throat, gastrointestinal manifestations, and headache were recorded in a separate checklist. All above clinical manifestations were evaluated on days 1, 2, 3, 4, 7, and 14. Cough in participants was evaluated using the cough frequency/severity scoring scale (17), which scored between 0 to 4 (0 for without cough and 4 for severe cough with chest heaviness). Body pain and weakness were recorded according to 0-10 scale in which 0 stands for without symptom and 10 for severe symptom.

The first interview was done face to face and necessary explanations were given to the patients. In the following days, the patients were interviewed by phone call.

Statistical analysis

The collected data were entered into the Statistical Package for Social Sciences version 26 (SPSS Inc., Chicago, IL, USA). Descriptive data, including mean (standard deviation) for quantitative variables and number (%) for qualitative variables, were used to describe the data. Data analysis was conducted using ANOVA and chi-square test. We used repeated measurement ANOVA to compare continuous variable between the two groups over the study period. To compare the qualitative variables, chi square test was done and P value less than 0.05 (two-tailed) was regarded as statistically significant.

Sample size justification

Given the goals and the type of this study, the citation was based on the Chinese clinical trial registry (18) in this field while taking into account the assumptions: the error of 5%, the power of 80%, the effect size of about 40% or the risk ratio of about three in the two groups, and the ratio of one to one in the two groups were all measured using the following formula:

$$n = \frac{2\overline{p}(1-\overline{p})(z_{1-\alpha/2} + z_{1-\beta})^2}{(\partial)^2}$$

Considering a five percent drop in total amount obtained from the computations, at least 120 patients in both groups were needed. It should be mentioned that the sampling method was a purposeful sampling method that was easily based on the purpose of the study. Accordingly, the investigators were present at the study time and started sampling from accessible referral patients to obtain the total sample size.

Results

Patients

A total of 200 eligible patients were enrolled in the trial from April 2020 till June 2021 and after considering the exclusion criteria, 5 patients were excluded due to pregnancy or lactation and sever respiratory disease; therefore, 195 patients were randomly selected and assigned to either receive oral MCT in the intervention group (n = 100) or just receive diet recommendations in the control group (n = 95). The patients were followed for at least 14 days after the diagnosis till being symptom-free in each group. Finally, the data of 64 patients in the intervention group and 86 patients in the control group were analysed (Figure 1).

The mean age of patients was 37.78 ± 12.42 years in the intervention group and 40.81 ± 13.23 years in controls (P = 0.231), with a total male distribution of 61.3%. Data on demographic characteristics are shown in Table 1. There was not any significant difference in baseline characteristics of the two groups.

There were 41 males (64.1%) in the intervention group and 51 males (59.3%) in the control group (P = 0.55).

Clinical efficacy

At the end, the treatment duration of the disease in the intervention group was significantly lower than controls (3.64 ± 2.643 days versus 5.79 ± 3.20 days, P < 0.001).

Figure 2 shows changes in the mean standard error of measurements (SEM) of symptom in the studied groups over the follow up period. The repeated measures ANOVA was used to compare primary endpoints in the two groups. The within group analysis showed a significant improvement regarding the mean body pain, weakness, respiratory rate, dyspnea, intensity of cough, headache, sort throat and gastrointestinal symptoms over the study period in both groups (time P < 0.001) (Figure 2). Comparing the two groups, there was a significant more improvement regarding frequency of cough (P = 0.015, F = 2.33), weakness (P = 0.006, F = 7.91), body pain (P = 0.007, F = 7.46) and sore throat (P = 0.03, F = 5.82) over the follow up. For other symptoms the difference between the two groups was not Significant.

Discussion

The present study found that administration of oral MCT, with sugar deprivation and diet modification, could diminish body pain, weakness, respiratory rate, dyspnea, intensity of cough, headache and sore throat in outpatients suspected of COVID-19. We presume that these results were due to the ketogenic effect of MCT as well as the sugar-free diet. Reviewing past research, KD significantly increases the number of gamma-delta T cells in the lung found in bronchoalveolar lavage (10,19-21). Moreover some studies show that MCT can increase cellular energy production and improve metabolism
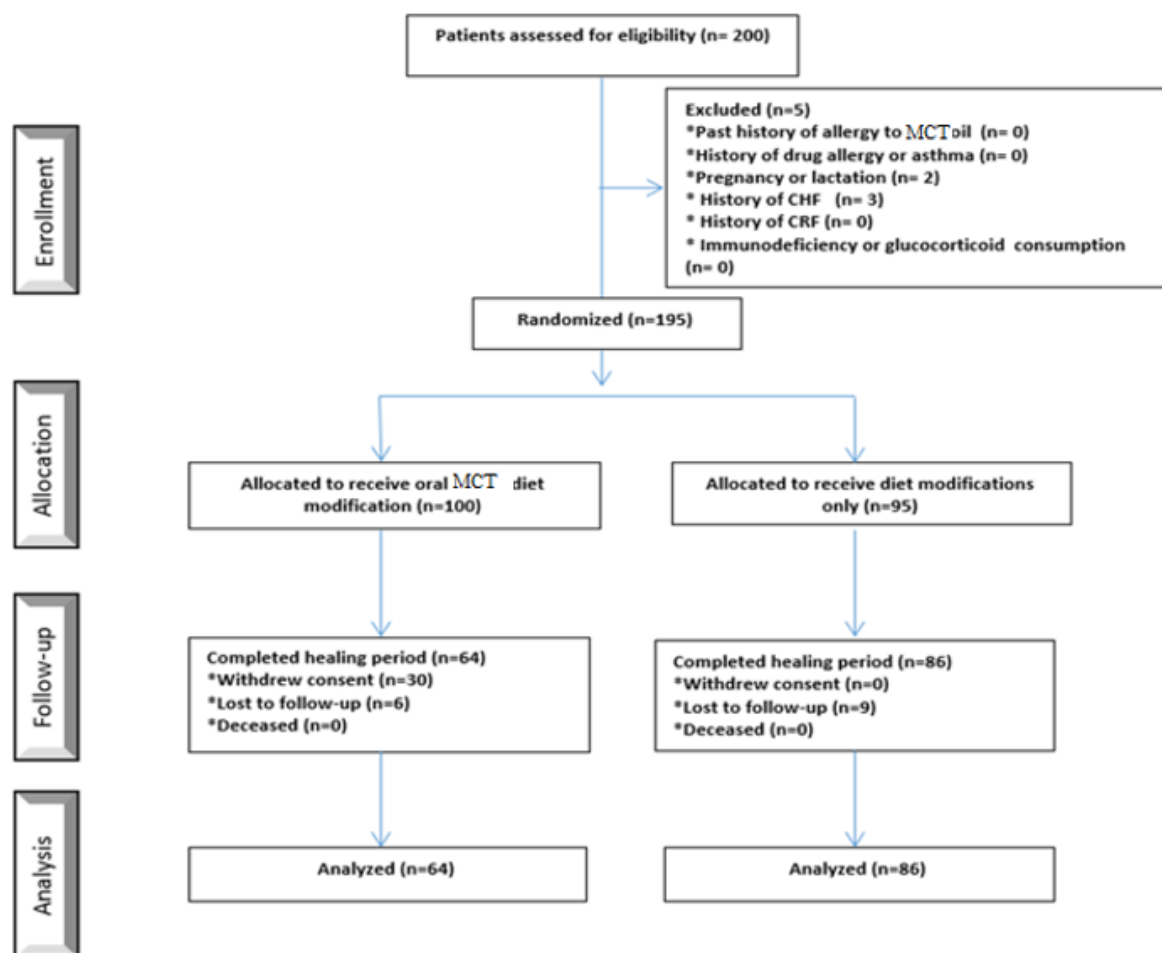
Figure 1. Consort flow diagram of the trial. CHF: congestive heart failure, CRF: chronic renal failure

Table 1. Baseline demographic characteristics of patients in the two groups

Parameter	Oral MTC (n = 64)	Controls (n = 86)	P value
Age (year)	37.78 ± 12.42	40.81 ± 13.23	0.231
Weight (kg)	76.42 ± 17.05	75.09 ± 10.75	0.914
Height (cm)	171.50 ± 15.97	158.65 ± 10.13	0.482
BMI (kg/m²)	26.11 ± 5.32	26.47 ± 3.68	0.642
Waist circumference (cm)	105.51 ± 11.84	101.65 ± 11.82	0.143
Cigarette smoking	55 (85.9)	13 (15.1)	0.857
Water pipe smoking	22 (34.4)	26 (30.2)	0.591

(22,23). On the other hand, according to the triggering of systemic inflammatory responses in COVID 19 disease, KD would be preventive for the progression of the cytokine storm syndrome (24). Arguably, Bradshaw et al declared that KD blunts cytokine storm in COVID 19 patients even by ingesting exogenous ketone supplementation (25), while some others, such as Goldberg et al did not find antiviral effects of the oral form of ketones, and declare that ketogenesis in the liver is more responsible for playing antiviral roles than oral ketone ingestions (10). In the present study, oral MCT was used and found effective in reducing the intensity of cough, weakness,

body pain and sore throat in COVID 19 patients. Also Dayrit investigated the in-vitro antiviral effects of lauric acid and its derivatives which consist of 50% of coconut oil and finally they suggested it as a safe and effective treatment for COVID-19 patients in the acute phase of the disease (26). The results of this study are consistent with the findings of the Angeles-Agdeppa et al study in Philippines. They evaluated the in-vitro effects of lauric acid and monolaurin on SARS-CoV-2, and also the clinical effect of virgin coconut oil on COVID-19 patients. They showed a significant reduction of patients clinical symptoms and some biochemical factors such as CRP and concluded that virgin coconut oil administration can improve all symptoms in suspected and probable COVID-19 patients (15). Our study was the first study on the administration of MCT in COVID-19 patients and its benefits in reducing disease symptoms. At the end of the study, none of the patients in both groups died, which could be due to the entry of mild and moderate patients into the study. This study evaluated the effects of oral MCT consumption on suspected and probable cases of COVID-19, which were followed up in the clinic on the first day and then on the following days through phone calls or virtual communication at home. Overall, the
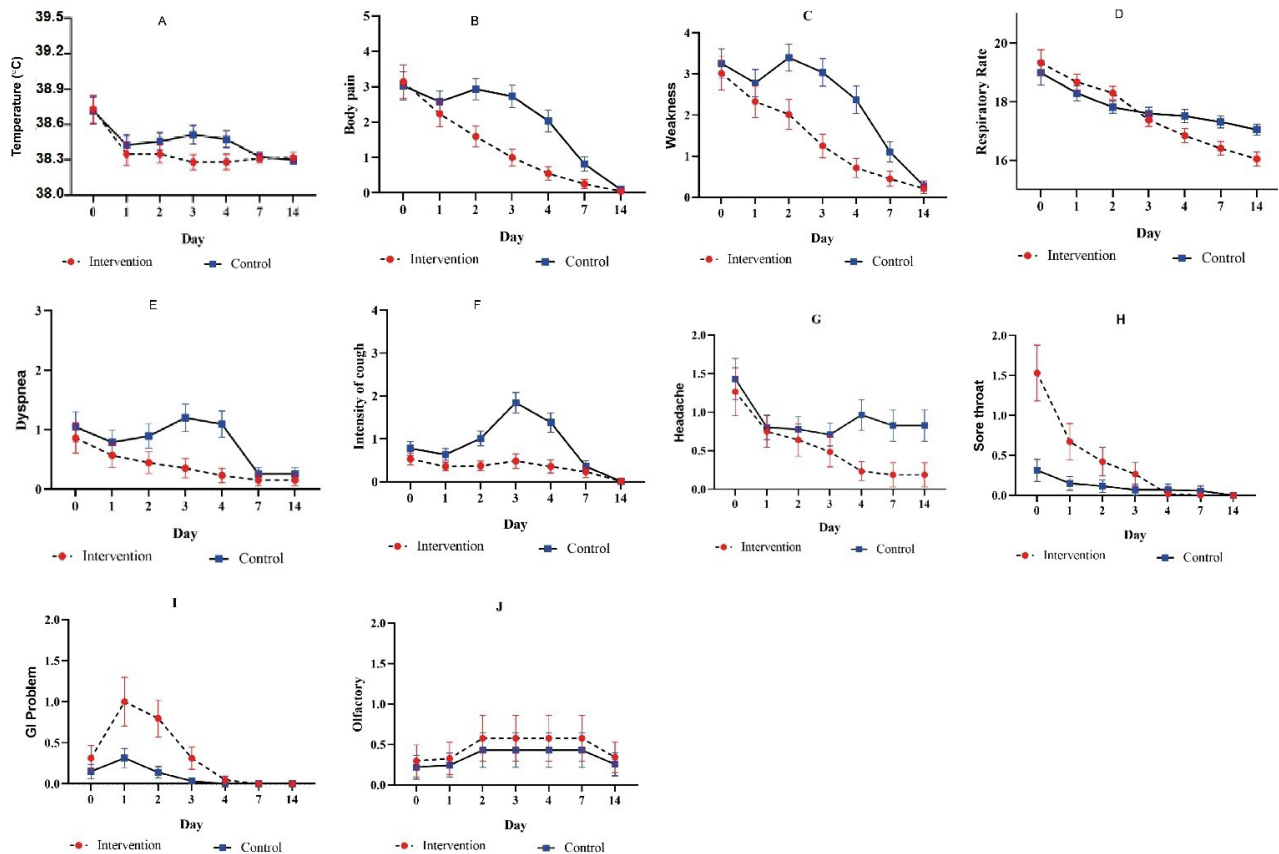
Figure 2. Changes in the mean, standard error of measurements (SEM) of symptom in the studied groups over the follow up period. The repeated measures ANOVA was used to compare primary endpoints in the two groups. The within group analysis showed a significant improvement regarding the mean body pain (B), weakness (C), respiratory rate (D), dyspnea (E), intensity of cough (F), headache (G), sort throat (H) and gastrointestinal (GI) symptoms over the study period in both groups (time $P < 0.001$).

MCT group showed faster relief of COVID-19 symptoms frequency of cough, weakness, body pain and sore throat, compared to the control group during 14 days. Gastrointestinal symptoms in the intervention group intensified from the second day onwards. This could be a side effect of the drug (MCT), as it has been reported in a research done on intestinal cells showing that MCT can damage the tight junctions of these cells (23). To reduce this complication, MCT should be mixed with food. These results are consistent with the antiviral and anti-inflammatory properties of MCT metabolites reported in laboratory and animal studies (27). There is another study conducted on nutrition and COVID-19 that found no benefit with high doses of ascorbic acid and zinc and a combination of the two (28). Therefore, it is concluded that the administration of micronutrients is less effective than ketogenesis induction in improving the symptoms of COVID-19 patients.

Limitations
We conducted this study without placebo control medication. Indeed, patients were not blind to the results and analyses that might increase the study bias.

In evaluating clinical symptoms, although standard questionnaires were used to assess patients equally, differences in perception and tolerance of terrible conditions by patients could affect our results and make them in bias.

Moreover, since dietary modification and sugar deprivation have also been performed, it is unknown how much MCT can affect on symptom improvement without these modifications. Therefore, we suggest further investigations with close patients` observations on confirmed cases to omit any confining factor. Also, we strongly recommend an investigation that evaluates the cellular and molecular effects of MCT oil on ketogenic pathway and immune system function.

Conclusion
In the present study, oral MCT was strongly effective in reducing clinical symptoms of SARS COV-2 infected patients and our results justified previous beneficial effects of KD in patients with viral respiratory tract infections. It may be considered a safe and available prescription in outpatient COVID-19 patients as an adjuvant therapy. Accordingly, MCT oil alleviated clinical symptoms of viral pneumonia cases and prevented probable disease morbidity.

Competing Interests

There is no conflict of interest to declare.

Ethical Approval

All steps followed COPE and Helsinki ethical codes. All participants in the study fulfilled informed consents form. This study was approved by the institutional review board of Kerman University of Medical Sciences with approval number of the Ethical Committee (IR.KMU.REC.1399.019). Likewise, the present study obtained IRCT registration number of IRCT20160313027033N2 (https://www.irct.ir/trial/46762).

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