Original Article

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Safety and Effectiveness of SeptimebTM in Patients with COVID-19 Referred to a Teaching and Referral Hospital: An Uncontrolled Clinical Trial Study (Phase II)

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Abstract

Background: We conducted this study to determine the safety and evidence of effectiveness of SeptimebTM among patients with COVID-19.

Methods: An uncontrolled phase II clinical trial with SeptimebTM was implemented in Imam Khomeini Hospital as a before-and-after trial during May to October 2020. Considering the inclusion and exclusion criteria, 33 patients with COVID-19 were treated using SeptimebTM. The patients received the anti-inflammatory drug 150 *mg* /10 *ml* /IV infusion SeptimebTM on the first day and then 300 *mg* /20 *ml* / IV infusion from the second day onwards for at least 2 days and up to 13 days based on the improvement of clinical symptoms and laboratory findings in addition to treatment which were selected according to the national protocol. The patients were then evaluated for the treatment efficacy and side effects. Adherence to treatment, clinical observations, and side effects were recorded before and after the treatment.

Results: The herbal drug SeptimebTM was injected in phase two of an uncontrolled clinical trial on 33 patients with COVID-19 in Imam Khomeini Hospital in Tehran as a before-and-after trial. The number of new cases admitted to the Intensive Care Unit (ICU) and the new need to Non-Invasive Ventilation (NIV) ecreased compared to before the treatment. Also, blood oxygen saturation and platelet count increased. Conversely, CRP, ESR, and ferritin levels decreased ($p<0.05$). Besides, SeptimebTM did not show any serious side effects except recurrent thrombophlebitis during the treatment.

Conclusion: We found some evidence regarding the efficacy of this drug and its low amount of short term side effects. The investigators recommend conducting the third phase of the clinical trial.

Keywords: Clinical trial, COVID-19, ICU, NIV, Laboratory profile, SeptimebTM

Introduction

On December 31, 2019, the first case of the novel coronavirus disease (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was diagnosed in Wuhan, China. Due to the nature of the virus, the unknown gene sequence, and its effects, the disease was recognized as a crisis by the World Health Organization (WHO). Clinical studies have been designed and implemented from the beginning of the spread to identify clinical, laboratory, and radiological symptoms of the disease, as well as therapeutic and preventive measures, and underlying factors. Due to the novelty of this virus and the absence of adequate information about the disease caused by this virus in humans, conducting epidemiological studies in communities affected by the SARS-CoV-2 virus is necessary to make them prepared to limit its spread and to identify and treat the patients (1).

Over the past 23 months, all countries around the world have contracted the disease. The first confirmed case of the COVID-19 virus in Iran was reported in February 2020 in Qom. The registered number of infected people has been reported to be about 5,899,509 so far (2). Due to the rapid spread of this disease, creating strategies to speed up the diagnosis of patients, isolating them from other patients to reduce the risk of disease transmission can be crucial (1). Since there was no history of the disease, most treatments received were experimental and based on clinical evidence. These treatments have been done using corticosteroids, antiviral drugs, oxygen therapy, and methods of controlling infectious diseases. Besides, reviewing the results of antiviral drugs that are effective on other similar viruses can help establish treatment protocols in COVID-19 patients (3). In Iran, the COVID-19 guideline for diagnosis and treatment of outpatient and inpatient services provided by the Ministry of Health and Medical Education (MOH&ME) is a resource for physicians to integrate into the selection of diagnostic and treatment methods for patients. However, the effectiveness of this guideline has not yet been determined and studies are needed to determine the treatment response of patients with COVID-19.

The inflammatory response plays an important role in COVID-19, and inflammatory cytokine storm raises the severity of COVID-19. CRP is a non-specific acute-phase protein aroused by IL-6 in the liver and a sensitive biomarker of inflammation, infection, and tissue damage. Cytokines are produced by steroid hormones, neuropeptides, and bacterial components (4). CRP expression level is usually low but rises rapidly and significantly during acute inflammatory responses. Zhu Z *et al* study presented that high level of peripheral blood cytokine IL-6, CRP and the existence of hypertension were independent risk factors for measuring the severity of COVID-19. The risk model established upon IL-6, CRP and hypertension had the most predictability value in this study (5). Velavan *et al* study illustrated that the consideration of low lymphocyte counts and the serum levels of CRP, D-dimers, ferritin, cardiac troponin and IL-6, may be used in predicting the severity and fatality COVID-19 in the hospitalized patients (6).

In this experimental study, we tested the safety of SeptimebTM for treatment of COVID-19 in conjunction with national treatment protocol. SeptimebTM, an injectable anti-inflammatory drug, is an herbal medicine that combines Tanacetum vulgare (tansy), Rosa canina, Urtica dioica extracts plus selenium, flavonoids, and carotene to inhibit cytokine cascade through the regulation of TNF-α, interferon-γ (IFN-γ), and IL-2. The drug is patented in Europe with the code WO/2007/087825 (7). SeptimebTM is a condensed form of the drug IMODTM, which is an immunomodulator. It is an herbal drug and a stronger form of IMOD. This drug is the combination of the extract of dog rose, Urtica dioica, Tanacetum vulgare, selenium, flavonoid, and carotenes (8,9). Tanacetum vulgare has anti-inflammatory effects. Urtica dioca most probably prevents the maturation of myeloid dendritic cells and reduces T-cell responses. Experimental studies have shown that SeptimebTM can regulate TNF- α, IFN- γ, and IL-2. In-vivo and in-vitro studies have demonstrated that IMODTM can also have a favorable effect on type-1 diabetes and inflammatory bowel disease (9,10).

Since a few medicines or vaccines have been approved for the definitive treatment or preventive goals of COVID-19 disease, the researchers intended to evaluate the safety and evidences of efficacy of SeptimebTM injectable anti-inflammatory drugs in patients with COVID-19 in Iran in the second phase of an uncontrolled clinical trial. In case of adequate

response to treatment and safety, the third phase of the clinical trial should be performed by considering the experimental and control groups and in a multicenter way.

Materials and Methods

Study design and participants

On the first day, SeptimebTM 150 *mg*/ 10 *mg* IVinfusion and then from the second day onward, SeptimebTM 300 *mg*/ 20 *ml* IV infusion was given to the patients for at least 2 days and a maximum of 13 days based on improvement in clinical symptoms and signs, and laboratory profiles. Blindness did not exist in this study, and it was done as an open-label. Since the main purpose of the study in the second phase of uncontrolled trial is to evaluate the safety of the drug, there was no control group (11).

A total of 33 patients were enrolled in the study. Twenty-four people (72.7%) were not in the Intensive Care Unit (ICU) before the treatment and nine patients (27.3%) were hospitalized in the ICU from the beginning. Of the nine patients in the ICU, six patients were in ICU before treatment and three patients were transferred to the ICU on the first day of the intervention, following the onset of worsening the clinical symptoms and signs prior to drug infusion.

Sample size

We used G-Power software to calculate the sample size and the sample size was 33.

T tests-Means: Difference between two dependent means (matched pairs)

Analysis: A priori: Compute required sample size

Input: Tail(s)=Two
Effect size dz=0.51
α err prob=0.05
Power(1-β err prob)=0.80

Output: Noncentrality parameter δ=2.9297269
Critical t=2.0369333
Df=32
Total sample size=33
Actual power=0.8107962

Inclusion criteria

We included the hospitalized patients in Imam Khomeini Hospital Complex of Tehran, which were adult (≥18 years old, both genders), confirmed COVID-19 with PCR test, and with moderate-or-severe diseases after filling written consent form during May 2020 to October 2020. Patients' hospitalization indications were based on management national protocol of COVID-19. All patients took standard care of COVID-19 based on the national protocol (O2 support, hydration, Dexamethasone 8 *mg*/IV/daily, Enoxaparin 1 *mg*/daily, Remdesivir 200 *mg*/stat and 100 *mg*/daily for 4 days and Famotidine 40 *mg* daily).

Exclusion criteria

Children, pregnant women, the patients under mechanical ventilation, cases with history of anaphylactic reaction, Chronic Kidney Diseases (CKD), Chronic Heart Failure (CHF), chronic hepatitis, vasculitis, malignant diseases, HIV and patients with negative SARS-COV-2 RT PCR were excluded. Moreover, patients who underwent convalescent plasma infusion and/or received tocilizumab were not included in the study.

Measurements

SeptimebTM drug included a 10 *ml* vial of 150 *mg* active ingredients content that was diluted in 500 *ml* dextrose water 5% and was given to the patients once within 1.5 hours in the form of infusion. In the absence of side effects, especially hypersensitivity reactions, 20 *ml* containing 300 *mg* active ingredients was diluted in 500 *ml* dextrose water 5%. The SeptimebTM drug was given to the patients for 2 to 13 days, depending on the clinical symptoms of each patient. The drug was discontinued after improvement of clinical symptoms (with doctor's discretion). The information about gender, age, underlying diseases, symptoms, signs, treatment duration, and hospitalization duration of the related questionnaire was recorded and kept confidential.

Primary outcome was length of hospitalization (general ward/ ICU days), the potential side effects (during three months of intervention) and mortality rate (after 3 months of intervention). Improving (during 14 days of intervention) symptoms and changes in inflammatory markers were secondary outcomes. All patients were daily checked in terms of improving or incidence of clinical symptoms and signs, recorded length of admission, laboratory

indexes, and need for hospitalization in ICU. After improvement of clinical symptoms with a doctor's discretion, the patients' medications were stopped. Blood samples for checking changes in inflammatory markers were collected before and immediately after stopping the drug. Potential side effects and mortality rate were followed up within and after three months of the start of the intervention.

Ethical considerations

The study was approved by the Tehran University of Medical Sciences (TUMS) ethical committee. After examination of entry and exit criteria and also obtaining informed written consent, patients were treated. Participation in this project was voluntary, and patients had to volunteer themselves for the treatment. Patients were allowed to refuse to cooperate with the study and follow-up whenever they wanted. However, in cases where patients did not refer for follow-up treatment and periodic evaluations, the research team followed up based on the patient's address and asked the reasons for not referring. If the non-referral was for reasons other than dissatisfaction and desire, efforts were made to eliminate it as much as possible and the treatment process continued.

All patients' information was considered strictly confidential. For this purpose, patients' records were kept in a safe place.

Statistical analysis

All collected data were entered into a computer and analyzed by software package SPSS, version 26 (IBM North America, New York, NY, USA). Quantitative findings were reported as mean and standard deviation and qualitative findings were reported as frequency and percentage. Parametric and non-parametric tests were used to compare before and after based on normality test. Considering the result of the Kolmogorov-Smirnov test, the Paired Samples T-Test, and the McNemar test were utilized to compare the difference before and after SeptimebTM administration.

Results

Descriptive findings

During this study, 92 patients were evaluated and 45 patients (48.9%) became candidates for participating, but finally a total of 33 patients (73.3%) included. Also, 3 individuals (9.1%) died during the study. About 79% of the participants were male and 21% were female. The mean and median ages were 53.7 and 54 years (18-79). The duration of the treatment varied from 2 days to 13 days with mean of 5.9 days. Besides, the maximum hospitalization period was 42 days and its minimum was 6 days by mean±SD of 16.0±7.95. The most common clinical signs before starting treatment included dyspnea (93.8%), fever (65.5%), and gastrointestinal (37.5%). Table 1 shows the demographic characteristics and clinical

Table 1. Demographic and clinical characteristics of the patients with COVID-19 treated by SeptimebTM at Imam Khomeini Hospital, Tehran, Iran

Variable	N(%)
Gender	
Male	26(78.8)
Female	7(21.2)
Underlying disease	
Diabetes Mellitus	13(39.4)
Chronic Lymphocytic Leukemia (CLL)	1(3.0)
Chronic Obstructive Pulmonary Disease (COPD)	2(6.1)
Chronic Kidney Disease (CKD)	2(6.1)
Asthma	1(3.0)
Cerebrovascular accident	1(3.0)
Hodgkin lymphoma	1(3.0)
Hypertension (HTN)	8(24.2)
Hyperlipidemia (HLP)	1(3.0)
Atrial Fibrillation (AF)	1(3.0)
Atrial Stenosis (AS)	1(3.0)
Interstitial Lung Disease (ILD)	2(6.1)
Psychiatric disorders	1(3.0)
Renal cell carcinomas	1(3.0)
Tuberculosis	1(3.0)
None	8(24.2)
Symptoms and signs	
Fever	21(65.5)
Dyspnea	30(93.8)
Gastrointestinal(GI)	12(37.5)
Seizure	1(3.0)
Loss of consciousness	1(3.0)
Age (yrs.)	
Mean±SD	53.7±13.2
Treatment duration (day)	
Mean±SD	5.9±3.1
Hospitalization duration(day)	
Mean±SD	16.0±7.95

Table 2. Laboratory findings of the patients with COVID-19 before and after the treatment at Imam Khomeini Hospital, Tehran, Iran

Variable	Before treatment mean±SD	After treatment mean±SD	p-value
ICU,n(%)	9 (29.0)	2(6.5)	0.039*
Non-invasive ventilation (NIV), n(%)	15 (48.4)	2(6.5)	<0.001*
O2 saturation (O2 sat)	79.90±7.90	91.58±3.96	<0.001*
White blood cell (WBC)	13216.13±12125.16	12977.42±17899.21	0.89
Lymphocyte count	2878.36±10275.21	4174.37±14933.52	0.17
Hemoglobin	13.53±2.06	13.35±1.97	0.48
Platelet	270500.00±109285.04	317500.00±150501.36	0.03*
C-reactive protein (CRP)	74.72±69.34	24.84±26.51	<0.001*
Erythrocyte sedimentation rate (ESR)	71.48±39.33	39.83±23.79	0.001*
D-dimer	2941.00±3078.96	1971.50±1577.23	0.50
Ferritin	1529.75±893.26	662.88±469.35	0.009*
Lactate dehydrogenase (LDH)	1094.20±621.57	984.00±540.90	0.50

*Statistically significant

symptoms and signs of the patients studied.

Safety and adverse events

Eleven patients (33.3%) were treated less than 5 days by Septimeb. The mean oxygen was 79.9 before the treatment and 91.6 after the treatment. Before treatment, six patients (18.2%) were under intensive care at the ICU and 15 patients (48.4%) were under Non-Invasive Ventilation (NIV). During treatment, 10 patients (30.3%) underwent NIV and in the first day of intervention, three of those who were under NIV, were transferred to the ICU. After treatment, two patients (6%) were under intensive care at the ICU; one patient was in the ICU before starting the treatment, and one patient went to the ICU during treatment. At the end of the treatment, none of the patients had fever, two patients (6%) had dyspnea, and two patients (6%) remained under NIV.

Examination of the results within 3 months in 33 patients has shown that the side effects of this drug were recurrent thrombophlebitis among seven patients (21.2%) which due to this complication, treatment with this drug was discontinued for the patients. Also, no side effects were observed on laboratory markers in any of the patients. There were no deaths three months after the treatment.

The patients all adhered to injectable SeptimebTM (100%). Regarding the evidence of the effectiveness of this drug among 33 patients with COVID-19 on ICU hospitalization, need for NIV and laboratory findings, analysis of the results with McNemar test showed that the number of ICU hospitalization (p=0.039) and new need of NIV (p<0.001) were significantly reduced after treatment with SeptimebTM. Also, T-test results indicated an increase in blood oxygen saturation (p<0.001), an increase in platelet count (p=0.03), a decrease in CRP (p<0.001), a decrease in the amount of ESR (p=0.001), and ferritin (p=0.009) compared to before SeptimebTM treatment. table 2 summarizes the status of these 33 patients before and after the treatment.

Discussion

It was found that by testing SeptimebTM drug on 33 patients with COVID-19 for at least 2 days and a maximum of 13 days, the rate of new ICU hospitalization and a new need for NIV reduced compared to before the treatment. Also, blood oxygen saturation increased and there was no death after

three months of intervention. This finding was in line with the findings of Eslami *et al*; they declared that SeptimebTM has positive effects on mortality rates in severe sepsis and showed that improved tissue oxygenation could be a reason for Septimeb's effect on reducing mortality rates (8). Douzinas *et al* suggested that lactate and cytokine production in sepsis was related to organ failure (12). Another study has shown that serum lactate, dependent on organ failure and shock, is associated with mortality rates in severe sepsis. Lactate is an unreliable indicator of tissue hypoxia in sepsis (9). In this investigation, lactate levels were significantly lower in the SeptimebTM group at the end of the intervention compared to the control group. Therefore, improving tissue oxygenation can be a possible mechanism in reducing sepsis mortality after drug intervention with SeptimebTM.

At the end of the treatment, the results of comparison of laboratory samples and inflammatory factors showed that platelet count increased, and CRP, ESR, and ferritin decreased ($p<0.05$). These changes also improved patients' clinical symptoms and signs. Results of studies indicated that IMODTM is safe and has no allergic and mutagenic ability (3,8,9). Most importantly, IMODTM potential effects in HIV positive patients on reducing the level of TNF-α and IL-2 have been represented (3). In this study, the CRP level after the treatment with SeptimebTM was very low. SeptimebTM seems to reduce inflammatory factors, but it is not noticeable due to the low number of patients and short follow-up period (6,13).

The evaluation of the results of this drug on 33 patients demonstrated that this drug has few side effects including thrombophlebitis, which is easily treatable, and no serious side effects were observed in total. This is notable because other existing treatments have many side effects compared to SeptimebTM. Thus, the SeptimebTM drug has far fewer side effects than many existing medicines. Also, this drug was effective in the patient's laboratory profiles. In addition, during the intervention, unstable and anaphylactic hemodynamic responses were not observed. Consequently, due to the significant effect of this herbal drug on disease treatment and on the level of lactate, the Sequential Organ Failure Assessment (SOFA), and the Glasgow coma scale (which are indicators of recovery in patients with sepsis), the use of SeptimebTM with standard treatment can be recommended (7). SeptimebTM may have a significant impact on reducing mortality rates, and if the follow-up period was higher, better results would have been achieved (13). Also, SeptimebTM may have a substantial impact on reducing hospital costs, since it is an herbal medicine and produced domestically.

In phase 1 of the clinical trial study on SeptimebTM safety assessment, male patients with HIV infection with CD4 levels above 200 cells/mm^3 in four cohorts of 3 people showed that up to 10 *ml* per day was tolerable for 4 weeks. Due to the lack of serious side effects related to Dose Limiting Toxicity (DLT) and easy tolerance of the doses received (5, 6, 7, and 8 *ml*) by these 12 patients with HIV infection, it seems that patients can tolerate up to 8 *ml* easily. In addition, by comparing CD4 levels before and after receiving the drug and observing a significant increase in CD4 in some of these patients, it can be found that this drug can significantly increase CD4 within two weeks (7). Pourdast *et al*'s study, which has been registered as a phase 1 clinical trial study of SeptimebTM, was aimed exclusively at accessing the maximum tolerable dose of the drug in human samples. The maximum dose of this study can be used to select therapeutic doses for other patients (8). Eslami *et al* findings have pretty much the same result as ours and the mentioned study. They have tested it on patients with sepsis and found that SeptimebTM illustrates positive effects on survival of the patients with severe sepsis, considering the withdrawal of activated protein C (6).

Follow-up of people with COVID-19 is particularly difficult in clinical trial studies. For various reasons, they may discontinue treatment, which should be encouraged by repeated follow-ups and incentives to take medication according to the doctor's instructions. Our findings are subject to several limitations. The number of participants in this study was low and the possible random error was not completely removable. The main limitation of the study is the absence of a control group, which in the design of the third phase of the study, this limitation has been removed by having a control group. The aim of this study was to observe the safety and efficacy of SeptimebTM in COVID-19 moderate and severe patients and to collect relevant

data to design third phase to compare the case group with the control group.

Conclusion

It seems that this drug has a few side effects, at least in the short term. Also, at this stage of the research, evidence regarding the effectiveness of this drug has been obtained. Thus, it is needed to further investigate the formulation of oral form and possibly the preparation and production of a new oral form because the injectable form has had significant effects on increasing blood oxygen saturation and platelet count among patients with COVID-19.

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Ethics Committee Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the Tehran University of Medical Sciences (protocol code IR.TUMS.VCR.REC.1399.041 and date of approval 8 April 2020). The project was registered in Iranian Registry of Clinical Trials (IRCT no.:20200324046847N1).

Informed Consent Statement

Informed consent was obtained from all the subjects involved in the study.

Data Availability Statement

Data is contained within the study.

Conflict of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of the data; in writing the manuscript, or in the decision to publish the results.

Sample Availability

Samples of the compounds are not available from the authors.

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