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Evaluation of the effectiveness of COVID-19 treatments performed in Iran in comparison with other countries: A review

Evaluación de la efectividad de los tratamientos COVID-19 realizados en Irán en comparación con otros países: una revisión

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Abstract

The treatment of COVID-19 has been one of the most important discussions in the scientific community for the last two years. Coronaviruses have seriously invaded human populations two times before December 2019 in the form of MERS and SARS diseases. Epidemiological findings show that the virus creates different and dangerous variants through new mutations, which make the definitive treatment more difficult. Molecular biologists have stated that as mutations continue, the vaccines would only provide immunity for one year, and the development of new vaccines should be on the agenda. But one of the major problems of developing countries is the lack of facilities such as vaccination, which has caused many problems for the medical staff in these countries. The findings showed that the use of some therapies, such as Remdesivir combined with standard treatment, has shown high therapeutic effectiveness; however, therapeutic side effects such as decreased glomerular filtration rate, decreased lymphocyte count, respiratory failure, and increased blood creatinine levels, have been observed in most patients. Also, paying attention to nutrition and immune-boosting factors can be effective in reducing the risk of contracting the virus.

Keywords: Corona medications, therapeutic efficacy, effectiveness of treatment, Covid-19, Coronavirus.

Resumen

El tratamiento del COVID-19 ha sido uno de los debates más importantes en la comunidad científica durante los dos últimos años. Los coronavirus han invadido gravemente las poblaciones humanas en dos ocasiones antes de diciembre de 2019 en forma de enfermedades MERS y SARS. Los hallazgos epidemiológicos muestran que el virus crea diferentes y peligrosas variantes a través de nuevas mutaciones, que dificultan el tratamiento definitivo. Los biólogos moleculares han afirmado que, al continuar las mutaciones, las vacunas sólo proporcionarían inmunidad durante un año, por lo que el desarrollo de nuevas vacunas debería estar en la agenda. Pero uno de los principales problemas de los países en vías de desarrollo es la falta de instalaciones como la de vacunación, que ha causado muchos problemas al personal médico de estos países. Los resultados mostraron que el uso de algunas terapias, como el Remdesivir combinado con el tratamiento estándar, ha mostrado una gran eficacia terapéutica; sin embargo, en la mayoría de los pacientes se han observado efectos secundarios terapéuticos como la disminución de la tasa de filtración glomerular, la disminución del recuento de linfocitos, la insuficiencia respiratoria y el aumento de los niveles de creatinina en sangre. Asimismo, prestar atención a la nutrición y a los factores de refuerzo inmunitario puede ser eficaz para reducir el riesgo de contraer el virus.

Palabras clave: Medicamentos contra Coronavirus, eficacia terapéutica, eficacia del tratamiento, Covid-19, Coronavirus.

Introduction

Coronaviruses (CoVs) are a group of enveloped viruses that cause various respiratory and gastrointestinal diseases in humans and animals[1]. Human coronaviruses cause one-third of colds in adults and in many cases cause mild diseases, but the new coronavirus (SARS_CoV-2) has become a dangerous virus by inducing new mutations in its genome. The virus binds to the antigens of squamous cells of the respiratory tract and causes pathogenesis[2-4]. The transmission rate of the new coronavirus is very high, and it is now affecting all countries of the world[5,6]. According to the World Health Organization, by mid-May 2021, more than 190 million people worldwide have been infected with the disease, of which about four million have died[7,8].

Age, underlying diseases such as heart failure, diabetes, chronic lung disease, hypertension, cancer, brain disease, kidney disease, liver disease, diabetes are among the underlying risk factors[9-14]. The virus is transmitted through respiratory droplets from sneezing and coughing, and the incubation period of the disease is about 7 to 14 days[15]. Considering the spread of patients and acute complications of the disease, evaluation of effective treatments in highly important.

In the present study, the author tries to provide effective treatment strategies by examining routine treatments inside and outside the country. For this purpose, in May 2021, an electronic research was performed in the scientific databases of Nature, PubMed, Medline and existing valid published articles, using the keywords of Corona medications, Therapeutic efficacy, Effectiveness of treatment, Covid-19, Coronavirus.

Clinical symptoms of Covid-19

The disease may occur with four different severities, namely mild, moderate, severe and critical patients (Acute Respiratory Distress Syndromes, ARDS)[1+]. The most common symptoms at the onset of the disease have been reported to be fever, cough, fatigue or myalgia, sputum, and headache. Among hospitalized patients, 32% develop acute respiratory distress syndrome (ARDS), 32% require intensive care, and 15% die[17,18]. Another study showed that approximately 20 to 30% of hospitalized Covid-19 patients, required intensive care for respiratory support due to pneumonia, of which 4.42% required advanced support of organs with endotracheal intubation and mechanical ventilation[13,19]. Although the virus majorly affects the respiratory and cardiovascular systems, neurological symptoms such as headache, dizziness, decreased sense of smell and taste, and nerve pain have also been observed in patients with severe symptoms[20]. Findings of computerized tomography (CT) scan of the chest also demonstrated bilateral involvement in most patients[21].

Transmission of Covid-19

Two main pathways are identified for the transmission of the coronavirus disease:

1) Direct transmission (through coughing, sneezing and inhalation of respiratory droplets)
2) Contact transmission (through contact with nasal, oral and ocular mucosa)[16].

Studies have shown that respiratory viruses are generally transmitted through respiration, and the coronavirus disease may also be transmitted from human to human through direct or indirect contact with respiratory droplets or through saliva[22]. The volume of the virus in the air is an important issue in the transmission of the virus so that in crowded environments, viruses adhere together as particles and are transmitted in large numbers[23]. New evidence suggests that the coronavirus is most often transmitted through respiratory droplets or microdroplets[24,25]. These cases indicate that attention to air conditioning will play an important role in reducing the risk of infection.

Certainly, paying attention to the factors that reduce the viral population is an important issue in reducing infection in hospitals. Studies show that the survival time of the virus is up to two days in chlorine-free water at 20°C, and this rate is much lower in chlorinated water. Survival of the virus on surfaces also depends on temperature, humidity, and light conditions. The virus is sensitive to sunlight and survives for a short time[26,27].

Common treatments

Domestic and foreign studies on medications and their therapeutic efficacy can be seen in **tables I** and **II**.

Foreign studies

In a study by Khan, Misdary et al.[28] on patients admitted to Robert Wood Johnson Hospital, 92 patients were analyzed, 30 of whom, from the first day of hospitalization, were treated with a standard dosage (10 mg) of oral montelukast once a day, and 62 patients in the control group did not receive the medication. The approved standard treatment of COVID-19 included the use of 400 mg hydroxychloroquine for 5 days and azithromycin. Patients receiving montelukast experienced significantly less clinical deterioration compared with controls (10% vs. 32%, respectively). The findings of this clinical trial showed that montelukast reduces the clinical severity of COVID-19 and could have a clinical effect in reducing the complications of this disease. With further evaluation, montelukast may be a potential treatment for COVID-19 infection[28].

Table I: Covid-19 treatments outside of Iran.

Foreign studies			
Type of treatment	**Study population**	**Treatment efficiency**	**Author(s)**
Montelukast combined with standard treatment	92 patients (30 in the treatment group, 62 in the control group)' the mean age was 67 years in the treatment group, and 59 years in the control group	Montelukast combined with standard treatment	[32]
Lithium carbonate combined with standard treatment	9 patients (6 people in the treatment group, 3 people in the control group). The mean age was 56 years in the treatment group and 65 years in the control group	Zero deaths in the treatment group and 1 death in the control group Decreased CRP, severe reduction in NLR, and decreased PLR	[33]
Tocilizumab (TCZ), a human monoclonal antibody, combined with standard treatment	65 patients (32 people in the treatment group, 32 people in the control group)' the mean age in the treatment group was 65 and in the control group was 60 years	5 deaths in treatment group and 11 in control group	[34]
Remdesivir combined with standard treatment	1062 patients (541 in the treatment group, 521 in the control group), mean age: 58.9±15	Mortality rate was 6.7% in the treatment group and 11.9% in the control group on day 15, and 11.4% in the treatment group and 15.2% in the control group by day 29. The most common unpleasant side effects that were observed in at least 5% of patients included decreased glomerular filtration rate, decreased hemoglobin level, decreased lymphocyte count, respiratory failure, anemia, pyrexia, hyperglycemia, elevated blood creatinine, and elevated blood glucose levels	[35]

In a study by Spuch, López-García et al., the effect of lithium carbonate on nine patients with severe COVID-19 infection was investigated. All patients received hydroxychloroquine for 5 days, and lopinavir-ritonavir as a combination therapy for 14 days. The findings of this study demonstrated that lithium carbonate significantly improved inflammatory activity and immune response in these patients by significantly decreasing the level of C-reactive protein (CRP) in plasma, increasing the number of lymphocytes, and decreasing neutrophil cells, and thus reducing the neutrophil to lymphocyte ratio (NLR); Similar to the NLR, the platelet-to-lymphocyte ratio (PLR) also decreased. It should be noted that lithium carbonate treatment improved all three parameters that were unchanged in the control group and no side effects related to lithium carbonate treatment were reported. All six patients who were treated with lithium carbonate survived, and one of the three patients of the control group died. They suggested that lithium carbonate treatment may be a new method for treating COVID-19 patients[29].

In another study, tocilizumab (TCZ), a human monoclonal antibody that targets the interleukin-6 receptor, was compared with the standard treatment of Covid-19. In all patients, for standard care, hydroxychloroquine 400 mg daily, lopinavir/ritonavir 100/400 mg twice daily, ceftriaxone 2 g for 6 days, azithromycin 500 mg daily, and subcutaneous injection of anticoagulant prophylaxis with enoxaparin 4000 UI once a day, were used. Tocilizumab was injected intravenously at a dose of 400 mg 24 hours after the first injection. On day 28, clinical improvements and mortality rates were not statistically different between the patients treated with tocilizumab and standard treatment. Bacterial or fungal infections were also recorded in 13% of tocilizumab patients and in 12% of standard treatment patients. They stated that there was no significant improvement in patients receiving tocilizumab compared to standard treatment, and in order to assess long-term risks, close monitoring on infectious side effects is required[30].

In a study by Beigel, Tomashek et al., 1062 patients were evaluated, of which 159 were in moderate condition and 903 were in severe condition of the disease (oxygen saturation ≤ 94%, respiration rate ≥ 24 breaths per minute). All patients received a standard care plan. Then, patients were randomly selected to receive Remdesivir (200 mg loading dose on day 1 and then 100 mg daily for up to 9 additional days) or placebo for up to 10 days or until discharge. Their data showed that Remdesivir reduced recovery time in adults, who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection, from 15 days to 10 days. Serious side effects, such as acute respiratory failure, were reported in 131 of 532 patients in the treatment group (24.6%) and in 163 of 516 patients in the control group (31.6%)31.

Domestic studies

In a study by Abbaspour et al., the effect of treatment with sofosbuvir / daclatasvir and ribavirin was investigated; 48 patients were divided into two groups of treatment and control, and the treatment group received sofosbuvir / daclatasvir once a day at a dose of 400.60 mg and ribavirin at a dose of 600 mg twice a day. According to the national guidelines, the control group received hydroxychloroquine (400 mg single dose) and lopinavir/ritonavir (400/100 mg twice daily),

with or without ribavirin (600 mg twice daily). The age group was between 18 and 80 years, and the severity of the disease was moderate (respiratory rate ≥ 24 breaths per minute; arterial O2 saturation < 94%; the manifestation of symptoms 8 days before admission, with consistent findings in chest CT scan). The study period was 21 days for the control group and 24 days for the treatment group. This randomized trial was too small for a definitive conclusion. Signs of improvement and reduced mortality were seen in the sofosbuvir/daclatasvir/ribavirin group. However, there was an imbalance in terms of basic features between different treatment groups. Larger randomized trials should be performed to further investigate this treatment process[36].

Another study examined the effect of convalescent plasma (CP) and standard treatment on Covid-19 patients. Patients were randomly divided into two groups for this clinical trial. Patients in the treatment group received one unit (500 ml) of convalescent plasma on the day of admission in addition to standard care, and the control group received only standard treatments. The mean age was 53.5 ± 10.3 years in the treatment group and 57.2 ± 17 years in the control group and the time of onset of symptoms was less than 7 days. Blood oxygen saturation was ≤ 93%, which was measured in room air. The results showed that the immune response was reduced in the plasma receiving group, but the length of hospital stay and mortality rate were similar in the two study groups[37].

In a study by Sadeghi et al., the effect of treatment with sofosbuvir/daclatasvir along with national standard care (hydroxychloroquine 200 mg twice daily with or without lopinavir/ritonavir 200/ 50 mg twice daily) was investigated. The mean age of patients was 58 years and they were selected from Shariati, Baharloo, Sina (Tehran), and Sayad Shirazi (Gorgan) hospitals. Patients with symptoms of moderate or severe COVID-19 infection were studied (fever above 37.8°C, respiration rate less than 24 breaths per minute, oxygen saturation below 94%, and the onset of symptoms in 8 days or less). The results showed that clinical improvements were observed in 29 of 33 patients (88%) in the treatment group and 22 of 33 patients (67%) in the control group, within 14 days of treatment; the average duration of hospitalization was 6 days for the treatment group and 8 days for the control group. The addition of sofosbuvir and daclatasvir to standard care significantly reduced the length of hospital stay compared to standard care alone. Although fewer deaths were observed in the treatment process, the difference was not statistically significant. Larger-scale trials are required to further investigate this treatment method[38].

In a study of Valizadeh et al. on patients with coronavirus disease, the treatment group received 160 mg of nano-curcumin daily in form of four 40 mg capsules for 14 days, and the control group received placebo capsules. In addition, all subjects in both groups received 300 micrograms of betaferon subcutaneously for up to 5 days, bromhexine 8 mg tablets every 8 hours, and atorvastatin 40 mg daily. Finally, the mortality rate in the nano-curcumin group was 20% (4 out of 20) and in the placebo group was 40% (8 out of 20). This study showed that nano-curcumin, by regulating the inflammatory response, may be used as an innovative therapeutic agent for COVID-19 patients, and might be able to reduce mortality, possibly by modulating cytokines in these patients[39].

The role of nutrition, vitamins, and antioxidants in the treatment

The most important role of vitamins is their positive effect on health and the strengthening of the immune system. Findings in Iran show that vitamins A B, C, D, and E have a positive effect on reducing mortality of COVID-19 patients[43].

B vitamins:

They are a group of vitamins that play a role in the metabolism of all cells. Vitamin B2 deficiency is widely

Table II: Covid-19 treatments inside of Iran.

Domestic studies			
Type of treatment	**Study population**	**Treatment efficiency**	**Author(s)**
Sofosbuvir 400 mg, daclatasvir 60 mg and ribavirin 1200 mg	48 patients (24 patients in the treatment group, 24 patients in the control group)' age range between 18 and 80 years	3 deaths were observed in the control group and no deaths were seen in the treatment group.	[40]
sofosbuvir/daclatasvir along with national standard care (hydroxychloroquine 200 mg twice daily with or without lopinavir 200 mg / ritonavir 50 mg)	66 patients (33 patients in the control group, 33 patients in the treatment group). The average age of patients was 58 years	3 deaths in the treatment group and 5 deaths in the control group	[38]
Study of the effect of convalescent plasma (CP); Donors were recovered individuals in the age range of 20-45 years with an asymptomatic recovery period of at least 2 weeks.	62 patients (in control and treatment groups) in the mean age was 53.5 ± 10.3 in the treatment group and 57.2 ± 17 in the control group	3 deaths in the treatment group and 5 deaths in the control group	[41]
Treatment with nano-curcumin	40 patients (20 in the control group, 20 in the treatment group)' age range between 19 and 69 years.	4 deaths in the treatment group and 8 deaths in the control group	[42]

observed in the elderly in the United States[44]. Also, Vitamin B3 or nicotinamide can boost the ability of immune cells to kill Staphylococcus aureus through a specific myeloid transcription factor and is effective in treatment[45]. In addition, vitamin B3 with a strong anti-inflammatory effect inhibits neutrophil infiltration into the lungs that are damaged due to ventilation[46]. Therefore, B vitamins can be used as a suitable option for reducing harmful microbes and boosting the immune system in selected patients. As mentioned, vitamin B2 deficiency has been observed in the elderly to a large extent, which is a highly important issue for this age group due to their vulnerability to coronavirus disease.

Vitamin D:

Vitamin D modulates adaptive immunity that plays an important role in the detection of viruses[47]. This vitamin regulates inflammatory responses of T helper cells by inhibiting the production of inflammatory cytokines IL-2 and interferon-gamma (INFγ)[48]. Serum vitamin D concentrations, which decrease with age[49], are an important factor in Covid-19 mortality rates in the elderly[14]. Also, vitamin D supplementation increases the expression of genes associated with antioxidants (some enzymes such as glutathione reductase)[50].

One study found that T cell levels were low in many COVID-19 patients and could be increased with vitamin D supplementation. In addition, vitamin D deficiency is associated with an increase in inflammatory cytokines and a significant increase in the risk of pneumonia and viral upper respiratory tract infections[51]. Vitamin D deficiency is associated with increased thrombotic events, which are often seen in patients with coronavirus disease. Also, vitamin D deficiency has been reported to occur more frequently in obese and diabetic patients, who are more likely to die from COVID-19[52, 53].

Therefore, due to the anti-inflammatory properties of vitamin D, it can be considered as a suitable option to reduce inflammation and increase the function of the immune system in treated patients.

Vitamin E:

Vitamin E as an antioxidant by binding to free radicals plays an important role in reducing oxidative stress[54]. Increased oxidative stress is observed in people with severe inflammation. Findings have shown the effective role of vitamin E supplementation along with other vitamins in reducing mortality in patients with coronavirus disease[43]. As a result, the use of antioxidants such as vitamin E in the diet of people exposed to the virus can be effective in boosting their immune systems.

Zinc:

Zinc is an essential substance in cellular functions and the development of the body largely depends on the presence of this substance. The immune system is greatly affected by the level of zinc in the body. Many enzymes and many important cellular proteins involved in biological cycles contain zinc in their structure. Zinc deficiency reduces the function of enzymes that are effective in inflammation and improvement of injuries and chronic diseases. Bone marrow stem cells require zinc to express immune genes and produce immune cells such as B lymphocytes[55-57]. The study of the effect of zinc in patients with coronavirus disease demonstrated that this mineral has been effective in reducing inflammation and cytokine response[58]. Certainly, measurement of zinc levels in patients and addition of zinc supplementation in the diet of patients can have beneficial effects on the prevention and treatment of COVID-19.

Nutrition and antioxidants

Antioxidants have beneficial structures that prevent further intercellular oxidation and inflammation, and this affects the metabolism and better function of cells[16]. Studies have shown that the use of antioxidants as adjunctive therapy in patients with Covid-19 has a beneficial effect on reducing the severity of the disease and improving the condition of patients[59,60]. Free radicals cause cytotoxicity and damage cells. Studies have shown that the use of herbal antioxidants, with a positive effect on the immune system, oxygen delivery, and glutathione levels in patients with lung diseases, reduces the time of mechanical ventilation, length of stay in the intensive care unit, length of hospitalization, and mortality rates; therefore, they can also help patients with coronavirus disease. However, for prescription, effective doses of herbal antioxidants should be considered[61]. Certainly, not all antioxidants provide a 100% recovery for patients with coronavirus disease, but this issue needs to be further investigated.

Immune System

Strengthening the immune system is probably one of the most important factors in improving the disease. The innate immune system is made up of mucus and the body's first defense layers, and the adaptive immune system directly detects pathogens and causes the death of viruses. Many studies have been performed on strengthening the immune system and, as mentioned, vitamins and nutrition are of particular importance in this field[43-54]. Findings show that COVID-19 initially affects the immune system by increasing the inflammatory response, and during the treatment process, attention to reducing the inflammatory response and increasing immune-boosting factors can be effective in reducing the severity of the disease and mortality rate[62].

Research has shown that all people who suffer from certain illnesses, even colds, are exposed to levels of cellular oxidative stress; reducing oxidative stress is an important issue in controlling inflammation, and antioxidants can be highly effective in this field[63-66]. As a result, strategies to reduce cellular stress in patients and the use of antioxidants would certainly be helpful in boosting the immune system and reducing severe cases of the disease. COVID-19[67-69], similar to many infectious diseases[70-80] caused serious morbidity among Iranians. However, diverse treatments have been reported in Iranian investigations[81].

Conclusion

The findings showed that the use of some therapies, such as Remdesivir combined with standard treatment, has shown high therapeutic effectiveness; however, therapeutic side effects such as decreased glomerular filtration rate, decreased lymphocyte count, respiratory failure, and increased blood creatinine levels, have been observed in most patients. Also, paying attention to nutrition and immune-boosting factors can be effective in reducing the risk of contracting the virus.

In addition, due to therapeutic expectations, the study and introduction of new drugs with greater effectiveness should be considered.

Interests conflict

The researchers declare that they have no conflict of interest.

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