Journal of Iranian Medical Council, Volume 6, Issue no. 2
http://dx.doi.org/10.18502/jimc.v6i2.12240

Original Article

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Investigation of Effective Drugs in the Treatment of Patients with COVID-19

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Abstract

Background: Due to the lack of definitive treatments for corona disease and the use of various medications in protocols around the world, it is necessary to conduct more epidemiological studies exploring the effect of different available therapeutic regimes; therefore, the present study aimed to explore the current effective drugs for the treatment of hospitalized COVID-19 patients.

Methods: The present study is a descriptive-analytical study that was conducted between August and September of 2021 at Khalkhal University of Medical Sciences. A convenient sampling method was employed to retrieve the data from the available hospital records, including 252 documents from COVID-19 hospitalized patients. A researcher-made checklist was used to record the data. Data were analyzed using SPSS 26 software.

Results: The findings showed that Hypertension and Hypotension (n=47,18.7%) are the most common underlying diseases in the study sample. The most therapeutic regimen was the combination of Remdesivir and Dexametason (n=137,54.4%) in hospitalized COVID-19 patients. There are a variety of organ involvements and presentations to the COVID-19; however, most patients experience a mild-to-moderate, self-limited disease; even though, the disease could progress to more fatal cases and lead to death.

Conclusion: The main pathology exists in the lungs which are caused by an inappropriate immune response that leads to a severe inflammatory response. Therefore, antiviral and anti-inflammatory drugs are currently the first-line therapy for hospitalized patients.

Keywords: COVID-19, Drugs, Medicine, Treatment, SARS-CoV-2

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Received: Jul 31 2022
Accepted: Jan 12 2023

Citation to this article:
Mehraeen E, Kianzad Sh, Matini P, Gharavi N, Heydari M, Karimi AA, et al. Investigation of Effective Drugs in the Treatment of Patients with COVID-19. *J Iran Med Counc.* 2023;6(2):307-14.

Introduction

In late 2019, signs of pneumonia with unknown sources in Wuhan, China was reported to the Chinese National Health Commission (1,2). Seven days later, a new virus, now called COVID-19, was identified and soon became a global health challenge and turned into a pandemic in March 2020 (3-5). Following logarithmic growth, the World Health Organization declared the prevalence of COVID-19 as a Public Health Emergency of International Concern (PHEIC) (6). Coronaviruses are a large family of viruses that cause respiratory infections in humans, including common colds, pneumonia, bronchitis, and acute respiratory distress syndrome (7).

The new coronavirus permeates and reproduces in the respiratory tract and involves the lungs. In almost 81% of patients, the virus causes only a mild disease; however, it could lead to severe disease in 14% of patients including pneumonia and shortness of breath and in 5% of cases leads to deterioration of the patient and causes death (8,9). Corona disease is a multi-organ illness and could cause severe complications including thrombotic complications, cardiac dysfunction and arrhythmia, acute coronary syndrome, acute renal failure, gastrointestinal symptoms, liver cell damage, hyperglycemia and diabetic ketoacidosis, neurological diseases, ocular symptoms and skin complications (10,11). There is currently no definitive treatment against it, and the drugs used against SARS-CoV-2 are mainly based on their effectiveness on previous species of coronavirus, namely SARS-CoV and MERS-CoV (12,13), and other treatments are often symptomatic (13). So far, various therapies such as antiviral sulfate, antimalarial drugs, corticosteroids, and other drugs have been recommended as potentially effective medications for the treatment of COVID-19 (14).

At the start of November 2020, only two appropriate anti-COVID-19 therapies, dexamethasone and remdesivir, had established a significant decrease in the length of hospital stay among COVID-19 patients (15,16). Guillaume *et al*, hypothesized that the use of these two treatments would result in reducing bed occupancy, hence playing a role in limiting the saturation of the healthcare system and diminishing the need for the strictest Non-Pharmaceutical Interventions (NPIs), such as lockdowns and curfews. Also, this study showed that the use of remdesivir would have a significant effect on hospital- and ICU-bed occupancy, even when administered only to patients with low-flow-oxygen therapy (16).

According to the related study, it is assumed that dexamethasone had an impact on the length of stay only for patients admitted to the ICU, with a 17% reduction in the ICU length of stay. This was based on the differences in the proportions of patients discharged from the hospital within 28 days conditional on being alive between the dexamethasone and placebo groups (17). The results of a study in England which was performed on 11500 patients demonstrated that low-dose dexamethasone, as a corticosteroid, could reduce mortality by approximately 30% in intubated patients and reduced mortality by 20% in patients using only oxygen (18).

The effectiveness of a combination of antiviral drugs including Ribavirin, Lopinavir, Oseltamiviror, and some antimalarial drugs such as hydroxychloroquine has been evaluated in other studies, but the effectiveness of these therapeutic drugs for the treatment of COVID-19 has not been yet proven (19). Remdesivir is one of these drugs that has already been used to treat Ebola (20). This drug is a monophosphoramidate and is considered as an adenosine analog and proven to have a wide range of antivirals activities in both non-human and human subjects (21). In the study conducted by Wang *et al* on 237 Chinese patients, intravenous Remdesivir did not significantly improve clinical recovery time, reduce mortality, or reduce virus clearance time compared with placebo (22). The results of another study conducted in the United States showed that Remdesivir improved 67% of the patients (23).

A study by Kai+ in China found that Favipiravir had fewer side effects than Lopinavir /Ritonavir and indicated a better therapeutic response to disease progression and clearance of the virus (24). Another group of drugs used to treat corona disease is corticosteroids, which are generally used to reduce inflammatory responses and acute lung damage. These drugs have been used to suppress cytokine overflow and immune responses during SARS-CoV-1 and MERS-CoV infection (25). Due to the lack of definitive treatments for corona disease and the use of various medications in protocols around the world, it is necessary to conduct more epidemiological studies

exploring the effect of different available therapeutic regimes; therefore, the present study aimed to explore the current effective drugs for the treatment of hospitalized COVID-19 patients.

Materials and Methods

The present study is a descriptive-analytical study that was conducted between August and September of 2021 at Khalkhal University of Medical Sciences. The standard checklist published by the World Health Organization was used to collect patient data (26). This checklist consisted of three parts and 45 items. The first part is associated with demographic information (11 items), the second part is related to exposure information (7 items) and the third part is related to clinical and therapeutic information (27 items). Due to the standardization of the tool, there was no need to check the validity and reliability of this checklist. The researchers completed this checklist by studing the medical records of people suffering from the COVID-19 disease.

The hospital records were included using a convenient sampling from all available hospital records that belonged to the COVID-19 patients. A total of 252 records were assessed. Inclusion criteria comprised positive PCR and confirmation of delta variant by laboratory tests. A researcher-made checklist was developed to gather the data related to the demographic characteristics of study participants such as age, sex (female and male), marital status (married, single), job (employee, student, health care personnel, farmer), type of underlying disease (cardiovascular, renal, respiratory, diabetes, cancer, hormonal, liver, neurological and blood diseases), inpatient unit (internal, ICU), length of hospital stay, discharge status (expired, recovered, referred to another hospital), history of smoking and pregnancy and the therapeutic regimens including one of the following drugs: Remdesivir, Actemra, Cinnagen, Favipiravir, Dexamethasone Hydroxychloroquine.

After collecting the data, the checklist items were entered into IBM SPSS statistics V26 and analyzed using descriptive statistics, bivariate correlation test and statistical tests such as determining the mean and standard deviation of the data and regression.

Ethics approval and consent to participate

The present study was extracted from the research project with code IR.KHALUMS.REC.1399.001 entitled "Investigation of effective drugs for people affected by Coronavirus disease 2019 (COVID-19)

Table 1. Frequency and percentage of demographic information of the research community

Demographic info	Items	Frequency (percent)
Sex	Woman	126 (50)
	Man	126 (50)
Marital status	Married	230 (91.3)
	Single	22 (8.7)
Nationality	Persian	9 (3.6)
	Turkish	242 (96)
	Tat	1 (0.4)
Smoking	Yes	30 (11.9)
	No	222 (88.1)
Underlying disease	Yes	94 (37.3)
	No	157 (62.3)

Table 2. Frequency and percentage of underlying diseases in the research community

N	Underlying disease	Frequency (percent)
1	Heart disease	33 (13.4)
2	Kidney disease	16 (6.3)
3	Respiratory disease	14 (5.5)
4	Hematologic disease	24 (9.5)
5	Diabetes	23 (9.1)
6	Hypertension/Hypotension	47 (18.7)
7	Cancer	15 (5.9)
8	Nervous disease	15 (5.9)
9	Skeletal disorders	1 (0.4)
10	Thyroid disease	20 (7.9)
11	Liver disease	3 (1.2)
12	Diabetes and Hypertension	20 (7.9)
13	Heart and Respiratory disease	21 (8.3)
Total		252 (100)

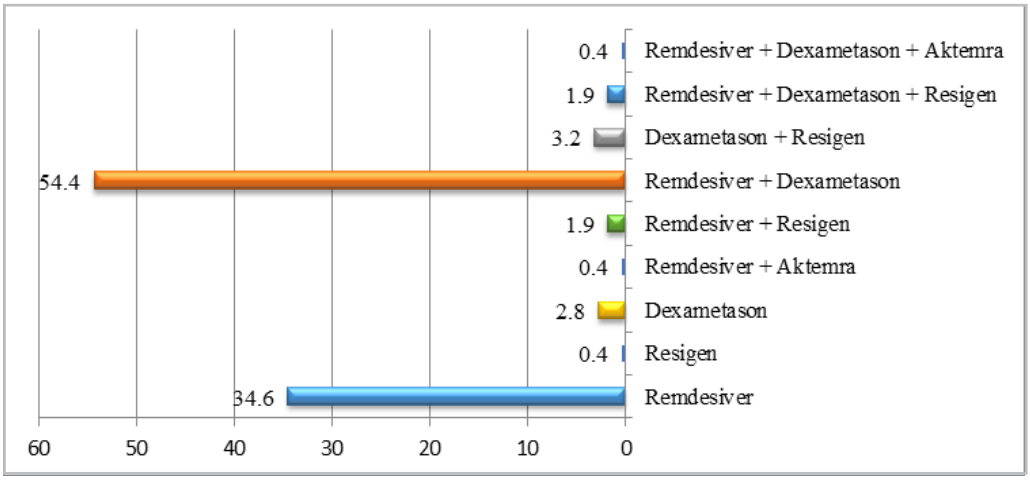

Figure 1. Percentage of the drugs used to treat the studied COVID-19 patients.

in Imam Khomeyni Hospital" conducted at Khalkhal University of Medical Sciences in 2021. We thank the statistical population and all the participants for taking the time to contribute to the study.

Results

We conducted a survey of current therapeutic options for COVID-19 patients and their relationship with the duration of hospitalization and patients' outcome. In this study, the information of 252 patients admitted to Imam Khomeini Hospital of Khalkhal was examined. The frequency and percentage of demographic information of these people are shown in table 1.

It appeared that Hypertension/Hypotension (n=47, 18.7%) are the most common underlying diseases among the study sample. The frequency and percentage of underlying diseases in the study population are shown in table 2.

The findings of the present study showed that the combination of Remdesivir and Dexamethason (n=137,54.4%) is the most common therapeutic regimen among the hospitalized COVID-19 patients. The percentage of drugs used to treat COVID-19 patients is shown in figure 1.

Based on the findings of this research, there was no significant relationship between drugs for the treatment of COVID-19 and contextual variables (p-value>0.05).

Discussion

The new coronavirus (SARS-CoV-2), which originated from Wuhan, China has led to a global pandemic. Most of the patients with COVID-19 have mild-or-moderate disease, however up to 5-10% present with severe and even life-threatening sickness. The mortality rates are approximately 2% (27).

Based on the pathological characteristics and diverse clinical courses of COVID-19, particularly in patients with moderate-to-severe COVID-19, the classes of drugs used in current therapeutic guidelines across the world include different combinations of antiviral agents, inflammation inhibitors, antirheumatic drugs, low molecular weight heparins, plasma, and hyperimmunoglobulin (28).

In this study, we aimed to discuss the most frequently used pharmacological agents among COVID-19 patients admitted to Imam Khomeini Hospital of Khalkhal, Iran that presented a favorable therapeutic profile against the SARS-CoV-2 infection in order to promote the current knowledge and inform the future guidelines for the treatment of the COVID-19 patients. During the critical period of the COVID-19 outbreak, the lack of definitive treatment for COVID-19 disease, and the use of various therapeutic protocols around the world, it is necessary to assess and evaluate a variety of possible options to treat the disease in order to reduce the morbidity and mortality of the virus. Our study findings showed that the combination of Remdesivir and Dexamethasone had the highest therapeutic impacts among the drugs used to treat COVID-19 patients and dwindle the duration of hospitalization and mortality in COVID-19 patients. Remdesivir, a nucleoside analogue prodrug, has an inhibitory impact on pathogenic animal and human coronaviruses,

including severe acute respiratory syndrome coronavirus2 (SARS-CoV-2) (22). Similar to our findings, Beigel *et al* showed that Remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection (20). Similarly, Malin *et al* found that Remdesivir could diminish the time to recovery by 31%, which is a relatively modest but clearly a favorite therapeutic effect (29). Besides these positive effects on patients, this may help to reduce the number of inpatient days, with positive effects on hospital costs and capacity issues that have occurred during the COVID-19 pandemic in several countries (29). Albeit, the study by Bartoli *et al*, in which 5-day versus 10-day Remdesivir therapeutic regimens were compared, failed to reveal better clinical outcomes depending on Remdesivir therapy duration, recommended that Remdesivir is the most effective antiviral drug available so far (30).

On the other hand, current evidence indicated that severely ill patients have a tendency to develop a pro-inflammatory condition, in which some cytokines such as interleukin (IL)-6 rise, compared to those who are moderately ill. The high level of cytokines also declared a poor prognosis in COVID-19. Moreover, excessive infiltration of pro-inflammatory cells, mainly involving macrophages and T-helper 17 cells, has been detected in lung tissues of patients with COVID-19 by postmortem examination. Recently, increasing studies suggest that the "cytokine storm" may contribute to the mortality of COVID-19 (31).

Glucocorticoid therapy is used extensively among ill COVID-19 patients with other coronavirus infections (*e.g.* SARS, MERS). Glucocorticoids exhibit pharmacologic effects at any therapeutically relevant dose through classic genomic mechanisms. Some immunosuppressive effects are based on transactivation, and glucocorticoid induces gene transcription and protein synthesis of NF-κB inhibitors and lipocortin-1. Through inhibition of NF-κB signaling, glucocorticoids encourage inhibition of synthesis of downstream proteins such as IL-1, IL-6, granulocyte-macrophage colony-stimulating factor, and inducible cyclo-oxygenase-2. Glucocorticoids reduce the proliferation, activation, differentiation, and survival of T cells and macrophages. Glucocorticoids extend inhibitory actions on the transcription and action of various cytokines. The Th1 and macrophage-based pro-inflammatory cytokines IL-1β, IL-2, IL-6, TNF-α, and IL-17 are subdued by glucocorticoids (32). Similar to our study, Fadel *et al* concluded that an early short course of methylprednisolone in patients with moderate-to-severe COVID-19 lessened escalation of care and improved clinical outcomes (33). Also, in a meta-analysis conducted by Prescott *et al*, the results indicated that administration of steroids is clearly associated with prognostic advantage among critically ill patients with COVID-19 (34).

However, there are also some studies with inconsistent results. The study performed by Moreno *et al* is an example of this controversy. The authors in this study warned against the widespread use of corticosteroids in all critically ill patients with COVID-19 at a moderate dose. Solely patients with more inflammatory levels could benefit from steroid treatment (35). Similarly, higher doses of dexamethasone not only failed to improve efficacy but also resulted in an increase in the number of adverse events and deteriorate survival in hospitalized patients with moderate-to-severe COVID-19 compared to the low-dose dexamethasone (36). Effective prevention and efficient treatment of COVID-19 requires further investigations and clinical interventions. One of the limitations of the present study was the impossibility of reviewing all drugs used due to the high variety of drugs.

Conclusion

COVID-19, the novel infectious disease caused by SARS-CoV-2 caused substantial human loss worldwide. The pathogenesis of this multi-systemic disease is not well defined yet. There are a variety of organ involvement and presentations in COVID-19, most patients experience a mild-to-moderate, self-limited course, however, in some patients, it could be fatal. The main pathogenesis exists in the lungs which are caused by an inappropriate immune response and subsequent cytokine storm. Therefore, the basis of most current therapeutic regimens consists of antiviral and anti-inflammatory drugs.

Acknowledgements

The present study was conducted in collaboration with Khalkhal University of Medical Sciences, Iranian Institute for Reduction of High-Risk Behaviors,

Tehran University of Medical Sciences, and Bergen University.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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