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Efficacy of Favipiravir and Remdesivir in the Treatment of Hospitalized Covid-19 Patients in Basrah, Iraq

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Abstract

A new coronavirus was identified as the cause of disease outbreak that originated from China. The virus is now known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 2019-nCov HCoV-19) and the disease is called Covid-19. There is no effective treatment for this disease; However, a few treatments such as favipiravir and remdesivir show some promising outcomes. Therefore, we conducted this study in order to evaluate the effectiveness of these drugs in reducing the length of hospital stay. Two groups of patients were studied at the Al-Mawani Hospital to investigate the effect of two different treatments in reducing the duration of hospitalization. A group received remdesivir (N=27) and the other one received favipiravir (N=19), in addition to the control (N=29). This is a randomized controlled trial that has been conducted to evaluate the effectiveness of remdesivir and favipiravir in reducing the hospital stay of Covid-19 patients. Length of hospital stay was measured in days. We found that both remdesivir and favipiravir are effective in reducing the length of stay of Covid-19 patients in hospital in comparison to the control, with more effectiveness for favipiravir than remdesivir. In addition to its efficacy against Covid-19, favipiravir has many advantages such as oral administration and low cost that made it more favorable to treat Covid-19, unlike remdesivir. More studies are warranted to reveal the most effective of the two treatments in terms of safety, use, and efficacy via including higher number of patients.

Keywords: *Favipravir, Remdesivir, Hospital stay, Covid-19*

1. Introduction

It is known that a group of serious respiratory diseases such as the common cold, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) are caused by a family of viruses that called Coronaviruses (Singhal, 2020). A new member of coronavirus family was identified in 2019 as a cause of respiratory disease outbreak that originally started in China (Singhal, 2020). The new one is now called the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 2019-nCov HCoV-19), and the disease caused

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by this virus is known coronavirus disease 2019 (Covid-19) (Rothan and Byrareddy, 2020). World Health Organization (WHO) announced that the Covid-19 outbreak has become pandemic from March 2020 (Abubakar *et al.*, 2016). This pandemic represents a very serious challenge to the whole world in last decades and has catastrophic effects which could continue for years (Rothan and Byrareddy, 2020; Abubakar *et al.*, 2016). The number of lost human's lives is increasing every day. In addition to the cost of lives and sever health disasters, a long standing economic down fold is witnessed around the world that will hugely influence the wellbeing of all populations in the coming years. Several measures that are now being used to overwhelm the pandemic could influence our lives in non-trivial ways in future (Singhal, 2020; Rothan and Byrareddy, 2020; Abubakar *et al.*, 2016).

So far, no effective treatment is found for Covid-19 patients, but a number of medications were showed some effectiveness at various levels of the disease and on different populations of patients (Gaurav and Al-Nema, 2019), and these treatments include (Sanders *et al.*, 2020; U.S. National Library of Medicine, 2020): Chloroquine and hydroxychloroquine; Anticoagulation; Azithromycin; Bronchodilators; Corticosteroids; Colchicine; Covid-19 convalescent plasma; Fibrinolytics; Immunomodulating agents; Inhaled pulmonary vasodilators; NSAIDS – The FDA continues to investigate the use of NSAIDs; Ivermectin and auranofin. In addition to FDA approved drugs or drug regimens (such as favipiravir, tocilizumab. arbidol, ribavirin, remdesivir, and lopinavir / ritonavir combination) are adopted for treating SARSCoV2 since they are able to target the RNA genome and angiotensinconverting enzyme2 (ACE2) receptors to block the replication of virus (Lou *et al.*, 2020; Clinical Trials Registry India. 2020; Murohashi *et al.*, 2020).

Favipiravir is an antiviral drug that with a potential to target Covid-19 viruses (Shiraki and Daikoku, 2020). This drug was firstly developed by Toyama Chemical Company, then later approved to treat influenza virus infection in Japan (Furuta *et al.*, 2013). Favipiravir, a derivative of pyrazine carboxamide, has antiviral effectiveness towards a wide range of RNA viruses (influenza virus, rhinovirus, and respiratory syncytial virus) (Yamamura *et al.*, 2020). This drug is metabolized to an active metabolite, favipiravir ibofuranosyl 52 triphosphate (T705RTP), which is a competitive inhibitor of purine nucleosides, preventing viral replication (Furuta *et al.*, 2013; Rattanaumpawan *et al.*, 2020; Clinical Trials Registry India, 2020).

Another antiviral drug with an activity against Covid-19 infection is remdesivir (Eastman *et al.*, 2020). Remdesivir was firstly reported by Gilead Sciences in collaboration with the Disease Control and Prevention (CDC) and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) (U.S. National Library of Medicine, 2020). This drug has a remarkable antiviral activity against Ebola virus as shown in clinical trials (Maldarelli *et al.*, 2020). It is also an effective therapeutic agent in vitro and in animal models of SARS and MERS coronaviruses (Maldarelli *et al.*, 2020). Remdesivir has a broad-spectrum antiviral activity since it is a nucleotide analog drug. It is used now to treat Covid-19 infection for adults and children with age 12 years and over whom their weigh at least 40 kg (Çalik *et al.*, 2020).

To our knowledge, there are no studies that compare the effects of favipiravir and remdesivir in the setting Covid-19 disease in Iraq. So that, we conducted this study in order to evaluate the effectiveness of favipiravir and remdesivir in the treatment of hospitalized Covid-19 patients.

2. Methods

The study of our research is about two drugs, remdesivir and favipiravir, that are used to treat Covid-19 patients. It is a randomized controlled trial conducted in Al-Mawani Teaching Hospital in Basrah City for the period between September 2020 and March 2021. The total number of patients was 75 at age range 25-47 years and they were randomly divided among groups. Patients that involved in the study were diagnosed as moderate cases as documented by the patient files in which physicians classified patients according to the severity of the symptoms and the duration of symptoms (more than 1 week). Study included three groups of subjects of both sexes: The first group (N=29) is control; The second group consists of 27 patients received remdesivir treatment (200 mg daily); And the third group consists of 19 patients treated with favipiravir (1800 mg orally twice daily on first day followed by 800 mg orally twice daily from day two and beyond). Groups of treatments was assigned by physicians as a non-blinded randomized controlled trial. Physicians discharged patients from the hospital when oxygen support was stopped and patient's recovery (faster recovery from symptoms). Patients with comorbidities such as cardiovascular disease, Diabetes, Coronary

Heart Disease, Hepatitis B, Cerebrovascular Disease, COPD, Cancer, and Children and pregnant women were excluded from the study.

In addition to the above treatments, patients could also take the following medications: Vitamin C; Vitamin D; Zinc tab; Paracetamol; Azithromycin; Dexamethasone; Enoxaparin; Ceftriaxone or Meropenem vial; Omeprazole; Bromhexine; and fluids (data not shown here).

The following test were done during the follow up: PCR test; CT scan; Urea / Urea Creatinine; TG / LDH; Glucose; S.ferritin; BCR / ESR; Cholesterol / HDL; Creative protein; D.dimer; L.F.T / R.F.T; RBC / CBC; TSB Rh factor; As.otiter; Calcium; Uric acid; body temperature; and oxygen saturation (data not shown here).

All the above tests were done according to the standards of Ministry of Health of Iraq and World Health Organization (WHO) (Singhal, 2021; Chinese Clinical Trial Register. 2020; U. S. National Library of Medicine. 2020). Briefly, body temperature was measured using digital thermometer (PIG, Germany). Oxygen level was measured using finger pulse oximeter (LED Digital Oxygen Monitor, China). Length of hospital stay was measured in days. All procedures were conducted under the approval of the College of Pharmacy in accordance with the University of Basra for the Care and Use of Laboratory Humans (IRB#5229).

3. Statistical Analysis

Data are shown as mean ± standard error of mean (SEM). We used unpaired Student *t* test to estimate differences. Throughout the analyses, a *p*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using the Excel package.

4. Results

Favipiravir and remdesivir are now used for Covid-19 patients in Iraq. However, there are no comparative studies that assess the effectives of these treatments in Covid-19 patients. These antiviral therapeutic agents are different in their costs, pharmacokinetics, and side effects profile. Therefore, we conducted this in order to compare the efficacy of these two drugs in Covid-19 patients. The results obtained through the study and

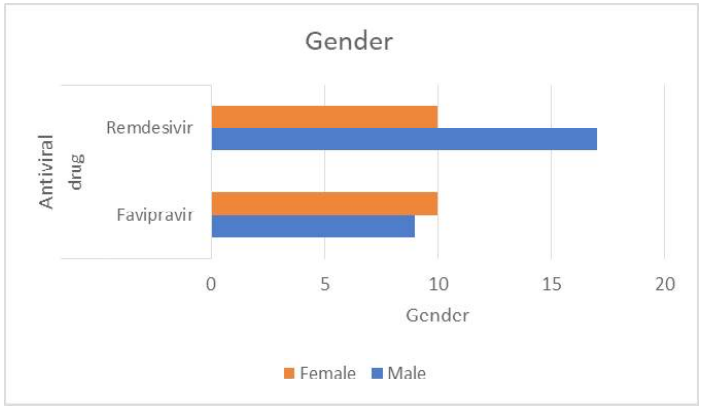

Figure 1: Gender of Patients who Received Favipiravir and Remdesivir

Table 1: Gender of Patients who Received Favipiravir and Remdesivir

	Drug	
	Favipravir	**Remdesivir**
Male	9	17
Female	10	10

follow-up of patients in the hospital showed that the number of women who received remdesivir is 10 and those who received favipiravir is 10 (Figure 1, and Table 1). While the number of men who received remdesivir is 17 and those who have received favipiravir is 9 (Figure 1).

The average age of the patients of two groups was almost similar. We found that the average age of patients received remdesivir is 52.2 years (Figure 2, Table 2). On the other hand, the average was 51.2 years for patients treated with favipiravir (*p* value = 0.8), suggesting no effects for age on the outcomes of the study (Figure 2).

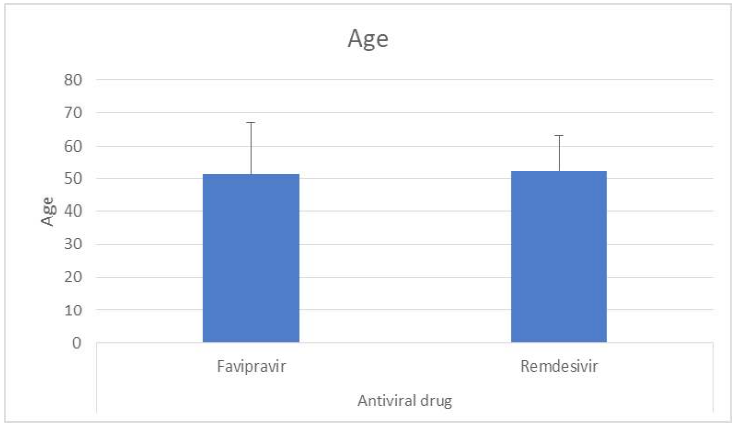

Figure 2: Age of Patients Treated with Favipiravir and Remdesivir

Table 2: Age of Patients Treated with Favipiravir and Remdesivir

	Antiviral drug	
	Favipravir	**Remdesivir**
Age	51.2	52.2
	15.9	10.7

We found also that the average of body temperature is not hugely different among patients of the two groups. The average of body temperature of patients received remdesivir is 38.64 ^{0}C (Figure 3, Table 3). While

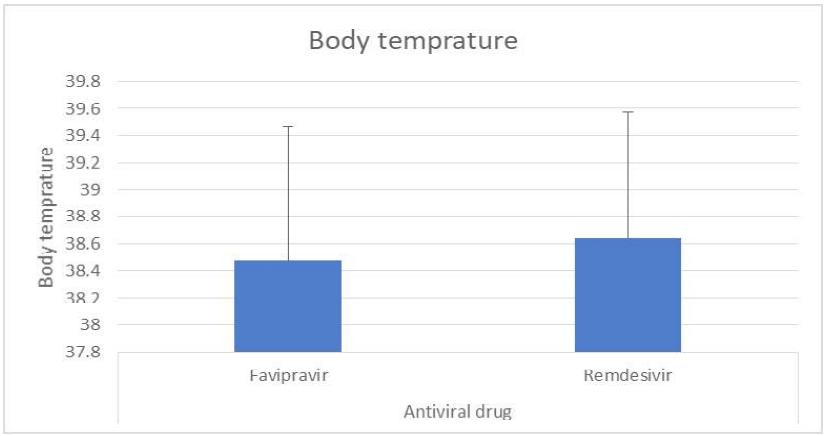

Figure 3: Body Temperature of Patients Treated with Favipiravir and Remdesivir at the Day of Hospital Admission

Table 3: Body Temperature of Patients Treated with Favipiravir and Remdesivir at the Day of Hospital Admission

	Antiviral Drug	
	Favipravir	**Remdesivir**
Body Temprature	38.47368	38.64
	0.993051	0.932952

it was 38.47^{0}C for those treated with favipiravir (*p* value = 0.58; Figure 3). This suggests that the severity of the infection in patients from the two groups was not different sensibly.

Moreover, we analyzed oxygen saturation in the patients of groups of treatments. We noticed that the average of SpO_2 in patients received remdesivir is 88.60 (Figure 4, Table 4). On the other hand, it was 90.31 in those who treated with favipiravir (*p* value = 0.41; Figure 4). All these parameters refer that the patients included in the study were in comparable levels of the severity of the infection.

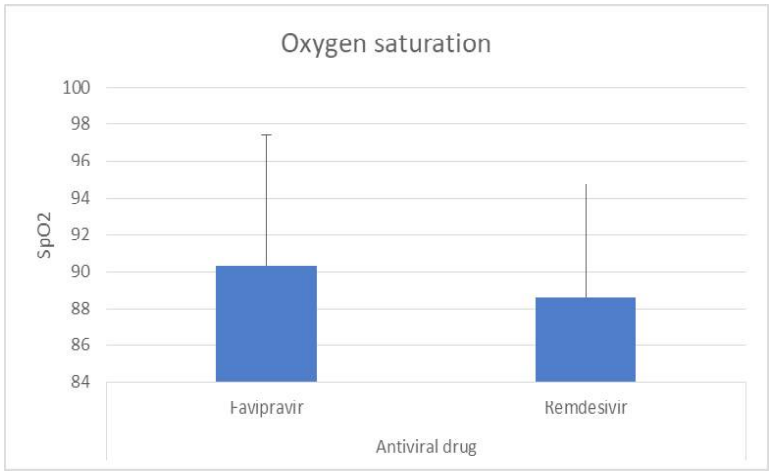

Figure 4: Oxygen Saturation in Patients Treated with Remdesivir and Favipiravir at the Day of Hospital Admission

Table 4: Oxygen Saturation in Patients Treated with Remdesivir and Favipiravir at the Day of Hospital Admission

	Antiviral Drug	
	Favipravir	**Remdesivir**
Oxygen Saturation	90.31579	88.60714
	7.130753	6.137352

Finally, we followed-up patients of the two groups for how long they stay in the hospital. We found that the average of the duration is 2.89 day for patients who received favipiravir (Figure 5). While it was 4.25 day for those who treated with remdesivir (Figure 5). The length of hospital stay was significantly different between the two groups (p value = 0.03). In addition, the length of hospital stay for patients from the groups of treatments was remarkably shorter if it compares with the control group (Figure 5). Collectively, these data suggest that both remdesivir and favipiravir are effectives treatments in reducing the duration that COVID-19 patients spend in hospital, with more favorable effect with favipiravir in comparison to remdesivir.

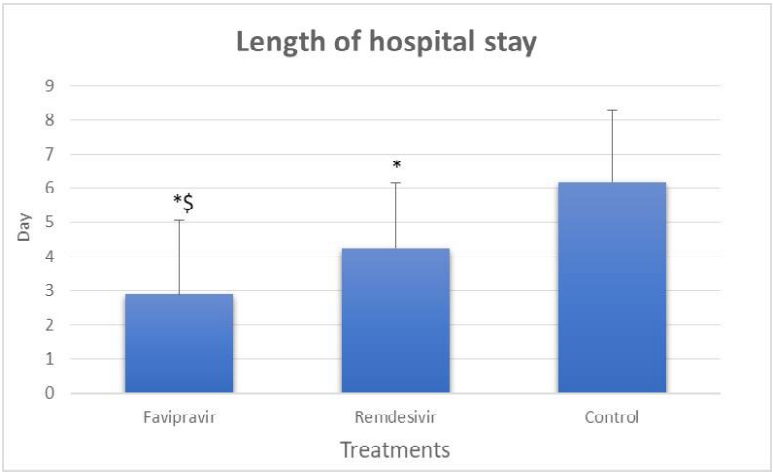

Figure 5: Length of Hospital Stay of Patients Treated with Favipiravir, Remdesivir and Control. * *p* value is significantly different from control. $ p value is significantly different from Remdesivir group

Table 5: Length of Hospital Stay of Patients Treated with Favipiravir, Remdesivir and Control. * *p* value is significantly different from control. $ *p* value is significantly different from Remdesivir group

	Antiviral Drug		
	Control	**Favipravir**	**Remdesivir**
Length of Hospital Stay	6.166666667	2.894736842	4.25
	2.130466824	2.181496865	1.88888

5. Discussion

Covid-19 has emerged as a severe threat to public health and also becomes an economic burden worldwide (Singhal, 2020). It is important to develop effective treatment strategies to control the pandemic as soon as possible (Carsana *et al.*, 2020; Chinese Clinical Trial Register, 2020). It has been used a lot of treatments for corona patients as we mentioned at the beginning (Sanders *etal.*, 2020; U.S. National Library of Medicine. 2020; Chinese Clinical Trial Register, 2020). The importance of this research lies in knowing the effectiveness and the safety of two antivirals, favipiravir and remdesivir, in treating Covid-19. Multiple clinical trials were conducted to evaluate the safety and efficacy of these drugs in Covid-19 patients (Behboodikhah *et al.*, 2022; Negru , 2022). So far, there is no evidence or scientific studies that fully prove the effectiveness of either of them in Iraq. The main goal of this study is to find out which of the two drugs is faster, more effective, and less time-consuming in treating Covid-19 patients. We found that favipiravir is better than remdesivir in terms of effectiveness, and duration of treatment.

In our research, we conducted this study with two groups of patients, one group received remdesivir and the other one received favipiravir. The results came as explained previously in Figures 1 to 4. These figures show that the cases severity was almost the same in all patients. This means there is no difference among patients who have received the treatment of remdesivir from those who received the favipiravir. Through the study, most cases of patients were average, and compared to research and articles, the condition of patients was from mild to moderate. The FDA has also authorized and approved the use of remdesivir and favipiravir for patients whose condition is mild to moderate (U.S. National Library of Medicine, 2020).

Regarding patients staying in the hospital, there was a remarkable difference in the duration of patient's hospitalization, as shown in Figure 5. Our data show that patients who received favipiravir had a shorter

treatment time course in comparison to remdesivir. Those patients stayed for much shorter time in the hospital, even though they were in a similar disease severity to those who received remdesivir. It is very likely that they improved with the first dose and discharged due to a faster recovery. The patient's stay in the hospital for favipiravir treatment was 1 up to 5 days. In contrast to remdesivir treatment, it ranged from 4 to 9 days. It is possible that the patients who have taken favipiravir treatment have a better recovery because the easy way of drug administration, oral compared to parenteral. It is known that oral administration is less stressful to the patients in comparison to the parenteral. It is also possible that the spectrum of favipiravir is broader than remdesivir in case of Covid-19. In terms of comparing the two treatments, there is no evidence studying their effects in a comparative manner (Lou *et al.*, 2020) until the time of this study.

The two treatments have good clinical outcomes, and covid-19 patients have recovered (Furuta *et al.*, 2013; Rattanaumpawan *et al.*, 2020; Clinical Trials Registry India, 2020; Maldarelli *et al.*, 2020; Çalik *et al.*, 2020) faster in comparison to no antiviral treatment. However, it is important to reduce the symptoms severity and the disease course in COVID-19 patients, especially if there is an infection in the lungs. For instance, studies have found successful outcomes so far with remdesivir, which has been approved in several countries (15-18). Positive data is also emerging on the possibility of favipiravir as a treatment for COVID-19, but still lacks sufficient evidence (Furuta *et al.*, 2013; Yamamura *etal.*, 2020; Rattanaumpawan *et al.*, 2020; Clinical Trials Registry India, 2020). While these emergent approvals and study developments on remdesivir and favipiravir are encouraging signs, it is important to monitor patients closely in a more detailed manner and report their outcomes or any unwanted side effects. In any case, studies are still ongoing research in order to reach to the most effective treatment with the safest side effect profiles (Negru *et al.*, 2022). In the future, we may find a study dealing with this prospective and comparing the two treatments comprehensively with a large number of patients from multi-centers trials.

In conclusion, it has been shown that favipiravir has a remarkable effectiveness against Covid-19 in addition to its attractive characteristics such as broad-spectrum antiviral activity, high oral bioavailability (>97%), self-administration, and relatively low cost. Unlike favipiravir, remdesivir should be given at hospital under supervision and it is a very expensive drug. We hope that our research will be a starting point for other research that compares more cases of patients on a large scale to get the best antiviral treatment for Covid-19 patients.

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