Evaluation of the effect of favipiravir in patients with COVID-19.

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Abstract

Background: Novel coronavirus disease 2019 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) started in December 2019 in Wuhan, China. A specific drug has been accepted for COVID-19 treatment. Favipiravir as an anti-viral drug affects RNA viruses like influenza and Ebola. Accordingly, the aim of this study is the evaluation of favipiravir effect on COVID-19 outcomes.

Method: This is a randomized controlled study including 97 patients with COVID-19 randomly allocated into favipiravir or control group. Primary outcomes were improvement clinical manifestations atrial oxygen saturation (SpO_2), and the secondary outcome was the length of hospitalization. Results: Clinical manifestations recovery of COVID-19 patients was better in favipiravir group and mortality rates were less than the control group (p=0.0001 of both). The level of blood oxygen saturation (SpO_2) was significantly higher in faviiravir group (p=0.0001). Mean lymphocyte count was lower in the control group (p=0.004). In addition levels of Blood Urine Nitrgen (BUN) were higher in favpravir group (P=0.033). Length of hospitalization was similar in both groups (p=0.586).

Conclusion: Favipiravir can be effective for clinical and laboratory improvement of COVID-19 patients and it is a promising drug for decreasing of mortality rate in these patients.

Keywords: Coronavirus disease, Favipiravir, Antiviral drugs.

Introduction

A recent pandemic of novel coronavirus disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged from Wuhan, China in December 2019 which was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) and had spread very quickly [1]. As of 19 September 2021 more than 200,000,000 infected cases and more than 4,000,000 deaths have been identified in the world. Fever, cough, dyspnea, myalgia, headache, chest pain, and gastrointestinal symptoms are the most common manifestations of COVID-19, respectively.

Additionally, lymphopenia and abnormal findings in chest CT scans like ground-glass opacity are frequent paraclinical detections in the patients [2]. Most infected patients experienced mild to moderate symptoms or may be asymptomatic. In contrast, severe COVID-19 pneumonia in the patients caused by rapid virus replication and cytokine storm is often associated with deterioration and death. Lower respiratory infection usually occurs in the patient as happened in Severe Acute Respiratory Syndrome CoV (SARS-CoV) and Middle East Respiratory Syndrome CoV (MERS-CoV) [3].

Although in December 2020, COVID-19 vaccination has been started for prevention, no specific treatment has been identified. SARS-CoV-2 is a single-stranded RNA virus that has a similar structure and a clinical manifestation to some other viruses like influenza, SARS, MERS, and Ebola [4]. Thus, some antiviral drugs such as favipiravir and Umifenovir were used for related infections can be useful for COVID-19 patients. Favipiravir is an RNA-dependent RNA polymerase (RdRp) inhibitor that has been approved for the treatment of influenza and Ebola viruses. RdRp is an essential catalyzer enzyme that has a role in RNA virus replication.

Most studies of favipiravir conducted *in vitro* and clinical evidence respecting the safety and efficacy of favipiravir is low. So, the aim of this clinical trial study is the evaluation of the effect of favipiravir on COVID-19 outcomes [5].

Case Presentation

This was a clinical randomized controlled trial that included 97 patients with confirmed-COVID-19 by Polymerase Chain Reaction (PCR) test. The current study was approved by the ethical committee of Arak University of medical science with approval number IR.ARAKMU.REC.1399.179. The study was registered in the Iranian Registry of Clinical Trials (IRCT) with the registration number IRCT20201028049175N1. This study was performed at Amir-Al-Moemenin hospital between January 2021 and May 2021.

- Patients were enrolled according to the inclusion criteria include:
- Adults with 18 to 95 years of age with confirmed COVID -19 infection by PCR test.

- Non-pregnant or lactating patients.
- Patients with moderate to severe infection mean SpO_2<80% or pAO_2<60 cm H_2O, severe respiratory distress (RR>34), hemodynamic instability, acid-base disturbance.
- Patients with allergic reactions or deterioration of clinical presentations, acute renal failure, and heart failure were excluded.

Written informed consent was obtained from all participants. 114 patients were enrolled and 17 were excluded because of refusing co-operation. The patients were randomly divided into two groups. Favipiravir group include 50 patients who received 600 mg of favipiravir added to their routine treatment, twice a day for 7 days or until discharge. The Control group contained 47 patients that just received the routine drug and standard treatment of COVID-19 protocol [6-8].

Demographic information of participants was achieved and all patients were observed and examined. Vital signs included respiratory rate, pulse rate, blood pressure, O_2 saturation (SpO_2), and temperature were recorded before and after the treatment. Chest CT scan and blood samples were taken for all of the participants. The biochemical analysis included CBC, ESR, CRP, and renal function test mean Creatinine (Cr) and Blood Urine Nitrogen (BUN) were taken before and after using of treatment [9,10].

The main outcomes of the study were mortality rate, levels of oxygen blood saturation (SpO_2), length of hospitalization, and ICU stay.

The sample size of the current study was calculated that favipiravir affected therapeutic responses include viral clearance and COVID-19 progression. Based on the study, with the following formula sample size were 57 patients in each group.

$$N = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 (\delta_1 + \delta_2)^2}{(\mu_1 - \mu_2)^2}$$

$$z_{1-\frac{\alpha}{2}} = 1.96 \qquad z_1 - \beta = 1.28$$

$$\delta_1 = 0.64 \qquad \delta_2 = 1.7$$

$$\mu_1 = 3 \qquad \mu_2 = 2$$

Statistical analysis

The normality hypothesis test for quantitative variables was the Kolmogorov-Smirnov test and these variables were expressed as the mean and standard deviation. Chi-squared test and Fisher's exact test were used for qualitative variables that were shown as percentages and numbers. Parametric tests include paired t-test and independent t-test was used for normal variables. Non-parametric tests include Mann-Whitney test and the Wilkinson test were used for abnormal variables. Covariance analysis test was utilized for evaluation of confounder's effect. Statistical significance of P value was under 0.05 and all of the analysis was performed by SPSS version 26 [11].

Results

The participants of both groups were matched in gender and age (p=0.790, p=0.142 respectively. There was no significant difference in vital signs including respiratory rate, pulse rate, blood pressure, O_2 saturation, and temperature between the two groups, but the levels of SpO_2 were significantly higher in favipiravir group (P=0.0001. ESR and CRP levels were similar in both groups. There were statistically significant differences in White Blood Cell (WBC count, platelet count, and Hb level between the two groups but it had no clinically significant as there were in normal ranges. Lymphocyte count was significantly lower in favipiravir group rather than the control group (p=0.004 [12]. The renal functional tests showed that there was no significant difference in the level of Cr between the groups but the BUN level was statistically significantly higher in patients who received favipiravir (P=0.033). In the evaluation of blood gases, there were no significant differences between the groups (Tables 1 and 2).

Table 1. *Baseline clinical and laboratory characteristics of the studied. Note: n: Number; SD: Standard Deviation; HB: Hemoglobin; WBCs: White Blood Cells; CRP: C-Reactive Protein.*

	Control (n=47)	Favipiravir (n=50)	P-value
	Mean ± SD	Mean ± SD	
Age in years	71.91 ± 15.87	34.86 ± 15.95	0.717
Hb	14.13 ± 1.99	12.86 ± 2.07	0.002
WBCs	8.54 ± 3.44	11.6 ± 16.15	0.367
Lymphocyte	10.62 ± 4.8	17.85 ± 11.19	0.004
Platelets	191.84 ± 67.03	232.42 ± 99.77	0.028
ESR	29.45 ±11.51	42 ± 39.59	0.085
CRP	1.25 ± 0.45	1.5 ± 0.57	0.409
Creatinine	1.22 ± 0.47	1.04 ± 0.42	0.815
BUN	24.23 ± 16.9	24.76 ± 16.5	0.033
ABG/VBG			
PH	7.32 ± 0.08	7.34 ± 0.19	0.406
PCO_2	34.68 ± 4.27	42.62 ± 20.61	0.54
HCO_3	19.07 ± 3.60	25.36 ± 7.07	0.017
	No. (%)	No. (%)	
Gender			
Male	26 (55.3)	29 (58)	0.79
Female	21 (44.7)	21 (42)	

Table 2. *Clinical outcomes of the two groups. Note: * N: Number; SD: Standard Deviation; O_2: Oxygen; SBP, Systolic Blood Pressure; DBP: Diastolic Blood Pressure; RR: Respiratory Rate; PR: Pulse Rate*

	Control (n=47)	Favipiravir (n=50)	P-value
	Mean ± SD	Mean ± SD	
Duration of hospital stay	10.53 ± 6.69	8.79 ± 3.85	0.586
Duration of ICU stay	16.57 ± 7.11	14.2 ± 9.85	0.539
Need for mechanical ventilation	3 (6.4%)	2 (4%)	<0.05
O_2 saturation	80.21 ± 10.43	90.6 ± 7.63	0.0001
SBP	113.19 ± 9.74	112.5 ± 14.07	0.951
DBP	72.23 ± 7.99	73.6 ± 11.15	0.554
Temperature	36.98 ± 0.74	36.67 ± 0.39	0.074
RR	21.18 ± 4.05	19.14 ± 1.95	0.019
PR	81.87 ± 10.49	78.14 ± 10.33	0.081
Patient condition			
Discharge	17 (36.2)	43 (86%)	0.0001
Mortality	30 (63.8)	7 (14%)	0.0001

Discussion

In this randomized controlled study about the effect of favipiravir on clinical manifestations in patients with COVID-19, we found that favipiravir can be associate with a higher level of SpO_2 in the patients and related to clinical improvement and decrease of mortality rate. In the current study, 30 patients in the control group (63.8%) and 7 patients in favipiravir group (14%) were expired that which showed the significant effect of favipiravir on COVID-19 mortality rate [13]. Additionally, a case-series study reported that combination therapy with favipiravir and Nafamostat mesylate can be useful for critically ill COVID-19 patients with scarcely mortality rates. Although few clinical studies have been tested favipiravir effect on COVID-19, some studies explained that cell virus entrance and virus replication were precluded in using favipiravir and pathologic responses leading to some events like hyper-coagulopathy can be prevented by combination therapy with Nafamostat mesylate. Also, we found that favipiravir can be effective for the clinical recovery of COVID-19 patients so that 86% of favipiravir group patients improved, whereas the lower percentages of the control group (36.2%) refined. In contrast, length of hospitalization and ICU stay were similar in both groups. Clinical and subclinical improvement in patients with COVID-19 in 7 and 14 days of favipiravir without significant side effects [14]. Additionally, a case-report study demonstrated that favipiravir related to the considerable effect on COVID-19 outcomes in a post-kidney transplant patient with severe pneumonia caused by SARS-CoV2. Although we reported that the levels of SpO2 were higher in patients who received favipiravir, patients' need for mechanical ventilation was similar in both groups. In contrast, a multicenter-randomized clinical study about the comparison of favipiravir and Chloroquine efficacy in COVID-19 outcomes reported that non-patients of favipiravir group needed mechanical ventilation and the length of hospitalization was lower than Chloroquine group. On the other hand, previous studies clarified favipiravir affects viral clearance. Open label clinical trial, the virus clearance was faster in patients with COVID-19 who received favipiravir than Lopinavir (LPV/ Ritonavir (RTV group. Promising effects of favipiravir including rapid viral clearance and significant clinical improvement without important side effects suggested that favipiravir can be considered for COVID-19 treatment. Additionally, a study based on comparison outcomes among patients who received favpiravir and Umifenovir treatment, showed that the clinical recovery including fever and cough improvement was significantly better in favipiravir group [15].

Favipiravir is an oral antiviral drug that roles as an RNA-dependent RNA-polymerase (RdRp inhibitor in RNA viruses. Favipiravir is a prodrug substance that returns to the active form after cell entrance then by attachment to viral RNA replaces purine nucleotide as the precursor of RdRp enzyme, so precludes the viral protein production and causes lethal mutagenesis of had important effect in influenza and Ebola treatment. Consequently, this is a promising condition to use of favipiravir for the treatment of the broad spectrum of RNA viruses in addition to influenza [16].

Conclusion

We investigated this study according to the need for more clinical trial studies with an admissible sample size for evaluation of favipiravir effect on the improvement of COVID-19 infection. The major strength of the current study was that this was a double-blind, randomized controlled trial, but it has some limitations that should be considered for future trials. First, clearance of the virus was not determined in the patients that it can be important to decide favipiravir results. Secondly, information about underlying disorders of patients was unknown. Lastly, the sample size was not enough for a definite conclusion, thus our findings cannot be generalized to all patients who receive favipiravir and we need more clinical trials with a large number of patients to receive more reliable achievement. Favipiravir can be effective in improving the condition of patients with COVID-19 and reducing patient mortality as well as increasing the level of arterial oxygen saturation; however, this drug did not affect the length of hospitalization and ICU stay. Based on the promising effects of this drug on the condition of patients, favipiravir can be considered as an effective drug on COVID-19.

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