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Original Article

A RETROSPECTIVE ANALYSIS OF TREATMENT OF COVID-19 WITH FAVIPIRAVIR

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Summary

One of the potential therapeutic agents for treating COVID-19 is favipiravir (FPV). This retrospective study compared the treatment of COVID-19 with (FVP group) or without (control group) favipiravir. Demographic characteristics and initial clinical indicators in the two groups were comparable. The level of oxygen saturation, respiratory rate, and prevalence of chest pain in the FVP group returned to normal significantly earlier (on the seventh day) compared to the control group ($p<0.05$). Improvement of patients' condition in the FVP group occurred significantly earlier than in the control group ($p<0.001$). In conclusion, FVP treatment's efficacy was higher than the control management strategy and established an individualized set of therapeutic agents. However, more detailed studies are needed to evaluate the efficacy of COVID-19 treatment with favipiravir fully.

Keywords: favipiravir, COVID-19, SARS-CoV-2, antiviral therapy, pandemic

Introduction

The outbreak of a novel coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 continues to spread worldwide and significantly impacts global public health [1]. As of July 13, 2021, the virus-infected people were over 186 million, resulting in over 4 million worldwide deaths [2]. In Kazakhstan, the number of confirmed cases was 494,222, and 4,997 deaths were recorded. However, there are no antiviral drugs with proven efficacy for the treatment of COVID-19, so the question of determining an effective, safe and affordable treatment strategy for this disease remains relevant. The following potential agents have been previously suggested: lopinavir/ritonavir, remdesivir, favipiravir, chloroquine, hydroxychloroquine, interferon, ribavirin, tocilizumab, and sarilumab [1,3].

One of the potential therapeutic agents for the treatment of COVID-19 is favipiravir (FPV). FPV (T-705) is a viral RNA polymerase inhibitor, earlier used for Ebola and influenza A

(H1N1) treatment strategy [4,5]. At the moment, there are several studies on the effectiveness of FPV in the treatment of COVID-19. In China, an open-label controlled study conducted by Cai et al. resulted in better therapeutic responses from FPV than lopinavir/ritonavir on COVID-19 in terms of disease progression and viral clearance [6]. One prospective observational study in Turkey showed that length of hospital stay, delay time, and symptom improvement were more significant in the FPV treated group. However, this could be because FPV was administered to patients who did not receive a first-line treatment [7]. Another prospective but randomized controlled multicenter trial that compared FPV with Umifenovir (Arbidol) did not find a significant difference in the clinical recovery rate on the seventh day of treatment [8]. One exploratory randomized controlled trial did not support adding favipiravir under the trial dosages to the existing standard treatment [9]. Based on preliminary results from phase II/III clinical trials, the Russian Ministry of Health granted FPV a conditional marketing authorization, making it the only approved oral drug for treating moderate COVID-19 to date [10]. Moreover, a systematic review and meta-analysis have shown significant clinical and radiological improvement after FVP treatment compared to standard treatment [11].

However, the effectiveness of FVP has not been fully understood. Moreover, there is no data on the use of FVP in Kazakhstan. Thus, this study aimed to expand the understanding of the effectiveness of treatment with FVP in fighting against COVID-19.

The purpose of the study was to explore the possibilities for expanding and new approaches in the treatment of COVID-19 and its impact on some health indicators. The coronavirus disease pandemic 19 is a disaster that has affected life worldwide, and achieving this goal would contribute to the overall effort to tackle this infection.

Materials and Methods

Due to the severe epidemiological situation caused by the COVID-19 pandemic, we conducted a retrospective study. The Local Ethics Committee approved the study of Astana Medical University (extract from minute No. 10, November 26, 2021).

The study involved patients with PCR-confirmed cases of COVID-19 of moderate severity. We included 80 patients in the study and divided them into two groups. Group 1 (experimental "FVP," n=40) included patients who received standard treatment (according to Clinical Protocol for Diagnosis and Treatment of Coronavirus infection COVID-19, approved by the Joint Commission for quality of medical services at the Ministry of Health, Republic of Kazakhstan, 2020) + FVP (the first day - 1600 mg/day, 2-10 days - 1200 mg/day under ECG monitoring). The control group 2 (n=40) received only standard treatment. The efficacy and outcome of the treatment were assessed by clinical indicators (temperature, oxygen saturation SpO2, respiratory rate, and heart rate), symptoms (weakness, cough, chest pain, shortness of breath, respiratory failure), and improvement in the patient's condition. These indicators were evaluated on the day of admission, the 7th day, and the 14th day of hospitalization. In addition, gender, age, days of hospitalization, and concomitant diseases were taken into account.

Descriptive statistics were performed by calculating the mean (M) and standard deviation (SD) for quantitative variables, and percentages were calculated for qualitative variables. The chi-squared test or independent sample t-test was used to assess the differences between variables. The cumulative improvement rate of symptoms and patient's condition between the FVP and the control group curves were analyzed using the log-rank (Mantel-Cox) test. Statistical analysis was performed using Microsoft Excel and IBM SPSS Statistics 20.0, and $p < 0.05$ was considered statistically significant.

Results and Discussion

Data were obtained from 40 patients from the FVP group and 40 from the control group. Table 1 presents baseline demographic initial clinical data of study participants.

As shown in Table 1, no significant difference was found in the distribution in the two groups by sex, average age, day of hospitalization, the prevalence of concomitant diseases, initial

Table 1. Initial characteristics of the study population (N = 80)

Characteristics	Group FVP (n=40) M (SD) / n (%)	Control group (n=40) M (SD) / n (%)	T-test / χ2	p
Gender				
Male	21 (52.5)	19 (47.5)	0.200	0.655
Female	19 (47.5)	21 (52.5)		
Age	51.1 (6.01)	53.6 (8.79)	1.44	0.154
Day of hospitalization	6.25 (2.75)	6.65 (2.32)	0.703	0.484
Comorbid conditions				
Diabetes mellitus	5 (12.5)	5 (12.5)	0	1
CVDs*	17 (42.5)	14 (35.0)	0.474	0.491
SPDs*	5 (12.5)	3 (7.5)	0.556	0.456
SpO2	95.7 (3.70)	96.4 (2.58)	1.09	0.281
Respiratory rate	21.4 (3.35)	22.4 (3,73)	1.36	0.179
Heart rate	87.3 (9.68)	88.8 (13.28)	0.568	0.572
Temperature	36.8 (0.70)	36.7 (0.74)	0.729	0.468

Note:
CVDs – cardiovascular diseases
CPDs – chronic pulmonary diseases

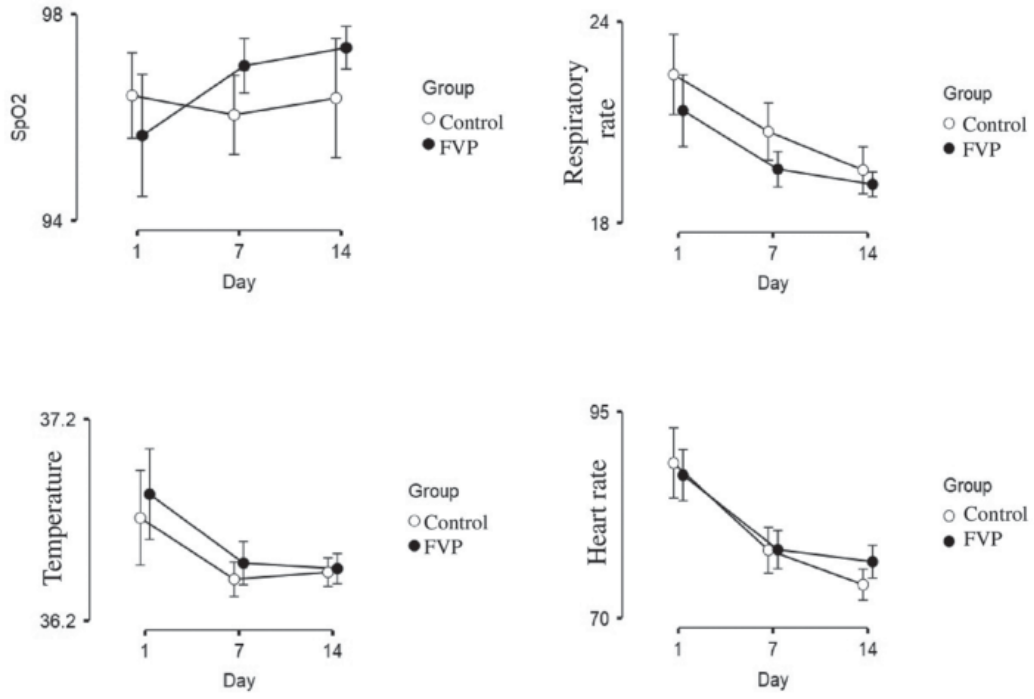

Figure 1. The dynamics of oxygen saturation, heart rate, respiratory rate, and temperature in the FVP and the control group

oxygen saturation, respiratory rate, heart rate, and temperature.

The dynamics of oxygen saturation, heart rate, respiratory rate, and temperature are shown in Figure 1.

The SpO2 levels did not show statistically significant differences between the two groups on the first day. On day 7, the SpO2 level was significantly higher in group FVP compared with the control group ($p < 0.05$). On day 14, the

SpO2 level did not reveal statistically significant differences in the two groups. However, in the FVP group, the 95% confidence interval was within the normal range.

On the first day, the differences between the two groups were not statistically significant. On the seventh day, the respiratory rate was significantly lower (which corresponded to the normal respiratory rate) in the FVP group compared with the control group ($p<0.05$). However, on the 14th day, no significant differences were found.

Heart rate and temperature were not significantly different on days 1, 7, or 14 of hospitalization in the two compared groups. However, both groups showed positive dynamics.

On no day was there a significant difference in the prevalence of weakness, cough, and chest pain symptoms. On day 1, the prevalence of dyspnea and respiratory distress was higher in the FVP group than in the control group. However, no significant differences were found on the following days. The reduction in the prevalence of symptoms of weakness, cough, shortness of breath, and respiratory distress in the two groups did not differ. However, a reduction in chest pain symptoms occurred significantly earlier in the FVP group. Nevertheless, regardless of the clinical presentation, the improvement in the FVP group occurred significantly earlier than in the control group, as shown in Figure 2 (Log-rank test $\chi2=27.5$, $p <0.001$).

The growing number of patients will have an impact on health systems. Thus, the contribution of this clinical practice work was to identify patients with signs and symptoms of prolonged

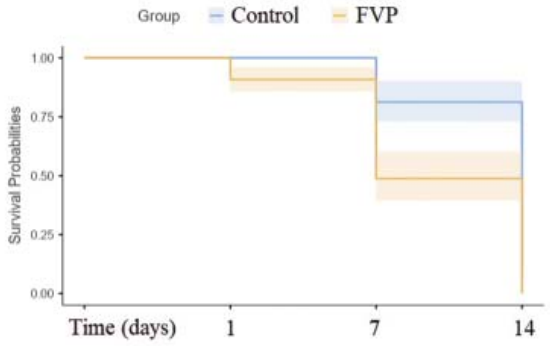

Figure 2. Survival curve of the improvement in the patient's condition in the FVP and the control group

COVID-19 in the primary health care system using a logged diagnostic process that examines possible etiology and establishes an accurate differential diagnosis and an individualized set of therapeutic agents.

Conclusion

This study compared the treatment of COVID-19 in an FVP and a control group. Initial demographic and clinical indicators in the two groups were comparable. The level of oxygen saturation and respiratory rate and the prevalence of symptoms of chest pain in the FVP group returned to normal significantly earlier (on the seventh day) than the control group. Moreover, improvement in the FVP group patients occurred significantly earlier than in the control group. These results warrant the assumption that the efficacy of the favipiravir treatment was higher than the treatment administered in the control group. However, more detailed studies are needed to evaluate the efficacy of favipiravir treatment fully.

References

1. Lu CC, Chen MY, Lee WS, Chang YL. Potential therapeutic agents against COVID-19: What we know so far. J Chin Med Assoc. 2020;83(6):534-6.
2. World Health Organization. Weekly epidemiological update on COVID-19 - 13 July 2021 [cited July 15, 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---13-july-2021
3. Mehta N, Mazer-Amirshahi M, Alkindi N, Pourmand A. Pharmacotherapy in COVID-19; A narrative review for emergency providers. Am. J. Emerg. Med. 2020;38(7):1488-93.
4. Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antivir. Res. 2013;100(2):446-54.
5. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil. Med. Res. 2020;7(1):11.

6. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering. 2020;6(10), 1192-8.
7. Çalık Başaran N, Uyaroğlu OA, Telli Dizman G, Özışık L, Şahin TK, Taş Z, et al. Outcome of noncritical COVID-19 patients with early hospitalization and early antiviral treatment outside the ICU. Turk. J. Med. Sci. 2021;51(2):411-20.
8. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. medRxiv. 2020. DOI: https://doi.org/10.1101/2020.03.17.20037432
9. Lou Y, Liu L, Yao H, Hu X, Su J, Xu K, et al. Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: An Exploratory Randomized, Controlled Trial. Eur. J. Pharm. Sci. 2021;157.
10. Ivashchenko AA, Dmitriev KA, Vostokova NV, Azarova VN, Blinow AA, Egorova AN., et al. AVIFAVIR for Treatment of Patients with Moderate COVID-19: Interim Results of a Phase II/III Multicenter Randomized Clinical Trial. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2020;ciaa1176.
11. Shrestha DB, Budhathoki P, Khadka S, Shah PB, Pokharel N, Rashmi P. (2020). Favipiravir versus other antiviral or standard of care for COVID-19 treatment: a rapid systematic review and meta-analysis. Virology Journal. 2020;17(1):141.
12. [Clinical protocol for the diagnosis and treatment of coronavirus infection COVID-19]. Protocol No. 107, Approved by the Joint Commission on the Quality of Medical Services of the Ministry of Health of the Republic of Kazakhstan dated July 15, 2020. Available from: www.gov.kz Russian.