Efficacy and safety of favipiravir plus interferon-beta versus lopinavir/ritonavir plus interferon-beta in moderately ill patients with COVID-19: A randomized clinical trial

Mehdi Hassaniazad1 | Hossein Farshidi2 | Abdollah Gharibzadeh3 | Ali Bazram1 | Elham Khalili4 | Afsaneh Noormandi5 | Mohammad Fathalipour6,7

1Infectious and Tropical Diseases Research Center, Hormozgan Health Institute, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
2Cardiovascular Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
3Social Determinants in Health Promotion Research Center, Hormozgan Health Institute, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
4Student Research Committee, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
5Department of Inpatient Services, Iran Food and Drug Administration, Tehran, Iran
6Department of Pharmacology and Toxicology, Faculty of Pharmacy, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
7Endocrinology and Metabolic Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

Abstract

Favipiravir (FVP), lopinavir/ritonavir (LPV/RTV), and interferon-beta (INF-beta) are considered as potential treatments for COVID-19. We examined the efficacy and safety of FVP and INF-beta compared to LPV/RTV and INF-beta combinations for the treatment of SARS-CoV-2. It was a single-center randomized clinical trial. Eligible patients were randomized to receive FVP plus INF-beta versus LPV/RTV plus INF-beta. The primary endpoint was the viral clearance after seven days of randomization. ICU admission, length of stay (LOS) in hospital, in-hospital mortality, and the incidence of adverse events were also measured. This trial was registered on the Iranian Registry of Clinical Trials (IRCT20200506047323N3). Patients were randomly allocated to the FVP (n = 33) and LPV/RTV (n = 33) groups. The viral clearance on Day seven was not significantly different between the FVP (31.1%) and the LPV/RTV groups (16.1%). The rate of ICU admission and likewise the in-hospital mortality in the FVP group (12.5% and 6.3%, respectively) were similar to the LPV/RTV groups (19.4% and 19.4%, respectively). The median LOS in the hospital was also not different (6.8 days [interquartile range; IQR = 5.0–11.0] in the FVP and 8.0 days [IQR = 5.5–12.5]) in LPV/RTV groups (p = 0.140). Adverse events were observed in 25.0% of FVP and 32.3% of LPV/RTV groups. The combination therapy with FVP did not exert a higher efficacy compared to the combination regimen of LPV/RTV. However, both treatment regimens demonstrated a mild profile of adverse events.

KEYWORDS

antiviral agents, interferon, SARS-coronavirus
1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the new coronavirus, has spread through the world and caused the recent pandemic of Coronavirus disease 2019 (COVID-19). The clinical symptoms of COVID-19 vary, including fever, cough, breathing difficulties, fatigue, and dyspnea. While the majority of patients with COVID-19 developed asymptomatic, self-limiting, or mild disease, the other patients progress to multiorgan failure, severe pneumonia, or even death. The World Health Organization (WHO) revealed that the COVID-19 pandemic formed a Public Health Emergency of International Concern (PHEIC) and provided temporary recommendations as advice under the International Health Regulations (IHR) On January 30, 2020.

Up to now, there is no effective pharmacological treatment for COVID-19, and the current standard regimens have demonstrated unreliable results. Some antiviral agents have been repurposed to manage COVID-19, including chloroquine, favipiravir, remdesivir, ribavirin, interferons (INFs), neuraminidase inhibitors, protease inhibitors, and hemagglutinin inhibitor.

Favipiravir (FVP) is a broad-spectrum, oral RNA-dependent RNA polymerase inhibitor approved for the treatment of influenza. It was also revealed the antiviral effects of FVP in the in vitro model of COVID-19. Several clinical studies have demonstrated the beneficial effects of FVP in the treatment of COVID-19, and WHO also entered favipiravir as a candidate trial therapy. Lopinavir/ritonavir (LPV/RTV) as a combined protease inhibitor has been approved by the US Food and Drug Administration (FDA) for the treatment of acquired immunodeficiency syndrome (AIDS). Moreover, it has also exerted antiviral function against Middle East respiratory syndrome coronavirus (MERS-CoV) and previous SARS-CoV. Nevertheless, the impacts of this combination for the patients with COVID-19 are unknown.

INFs have been used in clinical trials against SARS-CoV-1 and improved clinical outcomes. INFs, including INF-beta, INF-alpha express their antiviral effects through activating interferon-stimulated genes, decreasing vascular leakage, and improving ARDS complications. There have been various trials regarding the positive effects of INF-beta in patients with COVID-19.

Considering the high number of clinical trials carried out on FVP and LPV/RTV, there are still controversial data on the efficacy and safety of these medicines in patients with COVID-19. Additionally, there is limited information on combined regimens in the treatment of COVID-19. Thus, the present study aimed to evaluate the efficacy and safety of FVP and INF-beta combination compared to LPV/RTV and INF-beta combination in moderately ill patients with COVID-19.

2 | PATIENTS AND METHODS

2.1 | Settings

The study was an open-label, block randomized, phase 3 clinical trial with a parallel-group. This single-center trial was conducted at the Shahid Mohammadi hospital, Bandar Abbas, Iran. Ethics approval was received from the ethics committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.1399.225). The study was registered on the Iranian Registry of Clinical Trials (IRCT20200506 047323N3). The protocol of the trial was published previously.

The study was also undertaken in accordance with the guidelines of the Declaration of Helsinki and the principles of the International Conference on Harmonization Good Clinical Practice.

2.2 | Study population

All patients with age 18–80 years and confirmed diagnosis of SARS-CoV-2 based on the positive real-time polymerase chain reaction (RT-PCR) test in requirement of hospital admission due to an oxygen saturation (SpO2) ≤ 93% or respiratory rate (RR) ≤ 30 were eligible to enroll in the study. The time from onset of symptoms to randomization was not to be more than 7 days. Exclusion criteria included cirrhosis, chronic hepatitis, cholestatic liver diseases, chronic renal failure, peptic ulcers, known history of allergy to studied medicines, pregnancy, and lactation. Patients with severe infection (need for invasive or noninvasive ventilator support or shock requiring vasopressor support) were excluded. An informed and written informed consent was obtained from all participants.

2.3 | Randomization

Eligible patients were randomized in a 1:1 ratio to FVP and LPV/RTV groups. A stratified block randomization was used with a block size of six to create the randomization sequence. Sealed envelopes were used to protect the randomization sequence. A special code was allocated to every patient to conceal their identity, and patients were assigned to the groups based on their unique code.

2.4 | Intervention

Patients in the FVP group received 1600 mg favipiravir (Zhejiang Hisun) twice a day for the first day and 600 mg twice a day for the following 4 days. Patients in the LPV/RTV group received 200/50 mg lopinavir/ritonavir (Hetered Company) twice a day for 7 days. Five doses of 44 mcg interferon beta-1a (CinnaGen) every other day were also administrated to the patients in both groups. Another routine and supportive care were the same in both groups.

2.5 | Outcomes

The primary outcome was the viral clearance of SARS-CoV-2 in the nasopharyngeal samples assessed by RT-PCR after 7 days of randomization. The improvement in SpO2 (after 5 min discontinuation of supplemental oxygen), body temperature (temperature), and RR were
assessed during the intervention and after 7 days of randomization. Secondary outcomes were as follows: admission in intensive care unit (ICU), length of stay (LOS) in hospital, and in-hospital mortality. Improvement in clinical symptoms, including fever, chill, headache, sore throat, diarrhea, cough, fatigue, sputum, nausea or vomiting, myalgia, anorexia, taste and smell changes. The incidence of serious adverse drug events was recorded within 7 days of randomization.

2.6 | Statistics

The study sample size was calculated upon the assumption that the clinical improvement by Day 6 would be 80% in the treatment group and 35% in the control group, according to the previous studies. Considering a power of 80% and a significance level of 0.05, this study needed 26 participants in each arm. Accounting for a probable 20% dropout rate, 32 patients were required in each group.

Continuous variables were presented as mean and standard deviation, and categorical variables were expressed as frequency and percentages of patients in each category. Fisher’s exact test was used to compare viral clearance, ICU admission, mortality, and adverse drug reactions between the two groups. The daily values of \( \text{SpO}_2 \), temperature, and RR were compared between the studied groups using the generalized estimation equation (GEE) analysis considering the time, treatment regimen, and their interaction in this model. Moreover, LOS in hospital, temperature, and RR at the end of intervention were compared by the Mann–Whitney U-test.

The efficacy outcomes were assessed in the per-protocol population who had received complete treatment regimens. The safety outcome was studied in the per-protocol population as well as the intent-to-treat population who had received at least one dose of the medications. The SPSS version 18.0 (SPSS Inc.) was used for statistical analysis, and \( p < 0.05 \) was considered statistically significant.

3 | RESULTS

3.1 | Study population

A total of 91 patients with laboratory-confirmed SARS-CoV-2 infection were recruited, and after assessment of eligibility criteria, 66 patients were randomly allocated to the FVP (\( n = 33 \)) and LPV/RTV (\( n = 33 \)) groups. One patient in the FVP group and two patients in the LPV/RTV group were excluded from the study after randomization due to withdrawal of consent, and the remaining 63 patients completed the treatment regimen and were used for analysis as the per-protocol population (Figure 1).

The mean age was 53.75 years (SD, 13.48), and 36 (57.1%) patients were men in the per-protocol population (\( n = 63 \)). A total of 37 patients (58.7) had a body temperature of \( \geq 37.5^\circ C \) at baseline. Demographic criteria were not statistically different between FVP and LPV/RTV groups (Table 1). Baseline laboratory findings (Table 2) and clinical characteristics (Supporting Information file) were generally similar between the studied groups. A more significant improvement was seen in the FAV group regarding some clinical characteristics including, cough, fatigue, and smell change after 7 days of randomization.

3.2 | Efficacy

The viral clearance on Day 7 in the FVP group (31.1%) was higher compared to the LPV/RTV group (16.1%); however, the difference was not statistically significant.
Table 1: Demographic characteristics of the patients with confirmed COVID-19

|                | FVP group (n = 32) | LPV/RTV group (n = 31) | p     |
|----------------|-------------------|------------------------|-------|
| Age, years     | 50.97 ± 10.36     | 56.61 ± 15.75          | 0.100 |
| Sex, male      | 20 (62.5)         | 16 (51.6)              | 0.450 |
| Exposure history| 10 (31.3)         | 18 (58.1)              | 0.044 |
| Married        | 12 (37.5)         | 5 (16.1)               | 0.088 |
| Smoking        | 1 (3.1)           | 3 (9.7)                | 0.237 |
| Comorbidities  |                   |                        |       |
| Any            | 11 (34.4)         | 18 (58.1)              | 0.079 |
| Diabetes       | 4 (12.5)          | 9 (29.0)               | 0.129 |
| Hypertension   | 4 (12.5)          | 13 (41.9)              | 0.011 |
| Cardiovascular disease | 2 (6.3) | 7 (22.6) | 0.082 |
| Obesity        | 5 (15.6)          | 0 (0.0)                | 0.053 |
| Chronic lung disease | 1 (3.1) | 0 (0.0) | 0.999 |
| Rheumatologic disorders | 1 (3.1) | 0 (0.0) | 0.999 |
| Thyroid disorders | 1 (3.1) | 0 (0.0) | 0.999 |

Note: Values were expressed as mean ± SD or n (%). Comparison between groups was performed using the t-test or Fisher’s exact test. Abbreviations: FVP, favipiravir; LPV/RTV, lopinavir/ritonavir.

The results from the GEE model demonstrated that the changes in daily SpO2 (p = 0.460), temperature (p = 0.754), and RR (p = 0.125) in the per-protocol population had no significant difference between the two groups over hospitalization (Figure 2).

The LOS in hospital among medically discharged patients was 6.0 (interquartile range [IQR] = 5.0–11.0) days in the FAV group and 8.0 (IQR = 5.5–12.5) days in the LPV/RTV group (p = 0.140).

The rate of transfer to the ICU was 12.5% in the FVP and 19.4% in LPV/RTV groups (p = 0.509). Overall, there were eight deaths in hospital in the per-protocol population, two in the FAV and six in the LPV/RTV groups by Day 14 (p = 0.175). The clinical outcomes of the patients are expressed in Table 3.

3.3 | Safety

Overall, more adverse reactions were reported in the LPV/RTV group compared to the FAV group. Gastrointestinal reactions and leukopenia were the most prevalent side effects. However, there was no significant difference between FVP and LPV/RTV groups. Recorded adverse drug reactions in the studied groups are summarized in Table 4.

4 | DISCUSSION

Recently, enormous efforts have been conducted to reposition many drugs in the management of COVID-19 and diminish the complications of the disease. However, none of these possibilities have resulted in widely acceptable findings, and novel studies continue to be carried out. On the other hand, the development of vaccines and international vaccination campaigns has been more successful. However, the appearance of new genetic variants of the SARS-CoV-2 raises the thought that the COVID-19 pandemic will change to future seasonal epidemic waves in the near future. Antiviral treatments against COVID-19 will be required despite the worldwide vaccination.

The US FDA has approved the antiviral drug, remdesivir, for adults and certain pediatric patients with COVID-19. Many antiviral and anti-inflammatory drugs have also been authorized for emergency use including, nirmatrelvir and ritonavir combination, sotrovimab, bamlanivimab, casirivimab, and imdevimab. The urgency of the condition has led scientists to use antiviral agents.12 FVP, a prodrug and purine nucleoside analogue, selectively inhibits a viral enzyme RNA-dependent RNA polymerase and prevents replication of the viral genome can cause antiviral activity against RNA-carrying viruses.13 It has been approved for activity against new influenza viruses in China and Japan.14 It has also been effective against viral hemorrhagic fever and Ebola virus infections.13

However, society and organizational guidelines (World Health Organization guidelines, IDSA guidelines, National Institute of Health guidelines) have no recommendation using FVP in the control of COVID-19, given the different results of current clinical trials data.14 Moreover, the evidence regarding FVP showed controversial results in various clinical trials. Therefore the exact safety and efficacy of FVP need further clinical confirmation. Therefore, we decided to evaluate the safety and efficacy of FVP in an open-label, block randomized, phase 3 clinical trial with a parallel-group.

The obtained results demonstrated that clinical symptoms, including cough, fatigue, and smell change, improved significantly in the FVP group compared to the LPV/RTV group. However, other clinical symptoms had no significant differences between the two groups. A systematic review and meta-analysis of clinical trials conducted by Hassanipour et al.15 demonstrated that clinical symptoms improvement after 7 and 14 days in the FVP group were significantly higher than other treatments. Another meta-analysis conducted by Shrestha et al.13 showed that clinical improvement occurred after 7 and 14 days of treatment. Udwalid et al.14 showed patients in the FVP group significantly improved faster than another group.

In terms of imaging findings of radiological progression of lung damage/pneumonia, the results demonstrated that the studied parameters were significantly lower in the FVP group versus the LPV/RTV group. An experimental study conducted by Cai et al.1 demonstrated that chest CT changes were significantly improved after 14 days in the FVP group than the group receiving LPV/RTV.
| Characteristics          | FVP group (n = 32) | LPV/RTV group (n = 31) | p  |
|--------------------------|--------------------|------------------------|----|
| **Hematologic, $\times 10^9$/L** |                    |                        |    |
| Hematocrit Baseline      | 36.51 ± 3.84       | 34.43 ± 7.20           | 0.166 |
| Day 7                    | 36.58 ± 3.95       | 33.26 ± 4.17           | 0.021 |
| WBC Baseline             | 8.49 ± 4.10        | 6.45 ± 2.89            | 0.027 |
| Day 7                    | 7.78 ± 3.32        | 8.61 ± 4.07            | 0.568 |
| Neutrophil Baseline      | 74.51 ± 9.56       | 75.32 ± 10.34          | 0.748 |
| Day 7                    | 71.31 ± 21.32      | 81.81 ± 8.22           | 0.108 |
| Lymphocytes Baseline     | 16.80 ± 8.02       | 18.83 ± 9.08           | 0.351 |
| Day 7                    | 15.36 ± 9.29       | 12.09 ± 8.07           | 0.257 |
| Platelets Baseline       | 195.47 ± 72.02     | 208.67 ± 60.77         | 0.440 |
| Day 7                    | 246.77 ± 116.01    | 242.31 ± 99.62         | 0.901 |
| **Biochemical**          |                    |                        |    |
| Hemoglobin, g/L Baseline | 12.53 ± 1.77       | 11.45 ± 1.87           | 0.022 |
| Day 7                    | 11.94 ± 1.53       | 10.75 ± 1.54           | 0.027 |
| BUN, mg/dl Baseline      | 31.28 ± 8.77       | 38.07 ± 15.25          | 0.047 |
| Day 7                    | 37.31 ± 6.82       | 46.29 ± 20.96          | 0.081 |
| Creatinine, mg/dl Baseline | 1.04 ± 0.21        | 1.31 ± 0.44            | 0.005 |
| Day 7                    | 1.16 ± 0.24        | 1.17 ± 0.27            | 0.927 |
| ALT, units/L Baseline    | 44.90 ± 13.28      | 47.13 ± 21.27          | 0.628 |
| Day 7                    | 49.50 ± 13.92      | 64.58 ± 34.67          | 0.419 |
| AST, units/L Baseline    | 44.07 ± 12.48      | 54.97 ± 43.49          | 0.196 |
| Day 7                    | 42.75 ± 16.86      | 50.67 ± 22.30          | 0.529 |
| LDH, units/L Baseline    | 540.41 ± 299.70    | 610.97 ± 307.01        | 0.360 |
| Day 7                    | 599.33 ± 216.18    | 747.26 ± 303.35        | 0.224 |
| CRP (>3 mg/dl) Baseline  | 22 (68.8)          | 16 (51.6)              | 0.203 |
| **Coagulation function** |                    |                        |    |
| APTT, s Baseline         | 34.64 ± 5.43       | 39.72 ± 9.27           | 0.018 |
| Day 7                    | 47.00 ± 15.56      | 35.23 ± 9.83           | 0.148 |
| Pt, s Baseline           | 14.45 ± 6.30       | 13.93 ± 2.31           | 0.680 |
| Day 7                    | 14.70 ± 1.51       | 13.58 ± 1.34           | 0.209 |
| INR Baseline             | 1.07 ± 0.09        | 1.16 ± 0.32            | 0.194 |
| Day 7                    | 1.65 ± 0.84        | 1.07 ± 0.16            | 0.356 |
| **Imaging**              |                    |                        |    |
| Ground-glass pattern Baseline | 31 (96.9)          | 31 (100.0)             | 0.999 |
| Day 7                    | 12 (70.6)          | 28 (84.3)              | 0.011 |
| Consolidation Baseline   | 13 (40.6)          | 29 (93.5)              | 0.001 |
| Day 7                    | 5 (29.4)           | 26 (92.9)              | <0.001 |

Note: Values were expressed as mean ± SD, median (IQR), or n (%). Comparison between groups was performed using the t-test, the Mann–Whitney U-test, or the Fisher’s exact test.

Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood nitrogen urea; CRP, C-reactive protein; FVP, favipiravir; INR, international normalized ratio; LDH, lactate dehydrogenase; LPV/RTV, lopinavir/ritonavir; PT, prothrombin time; WBC, white blood cell.
The viral clearance after 7 days of hospitalization was not significantly different between the two groups, which could be due to inappropriate duration and dose of treatment with FVP. The dose of FVP in critically ill patients is controversial and recent data showing lower serum levels of FVP in these patients than in less severely ill ones. Hassanipour et al. also showed that the viral titer on the 14th of treatment in the FVP group was significantly lower than the group receiving LPV/RTV. However, they showed that the differences were not statically significant on the seventh and 10th days of treatment. Hassanipour et al. also showed that the viral clearance was significantly faster in the FVP group than in the LPV/RTV group.

Cai et al. also showed that noninvasive mechanical ventilation and requiring oxygen therapy was less in the patients receiving FVP.

Our analysis revealed the need for ICU admission LOS in the hospital was not statically different between the two groups. Khamis et al. also showed the need for admission in ICU was not statically significant between the FVP and hydroxychloroquine groups. Additionally, Lou et al. showed only one patient in the baloxavir marboxil group, and two patients in the FAV group needed ICU admission within 7 days of starting treatment. Based on our results, there have been no differences in in-hospital mortality on Days 7 and 14 between the two groups. Dabbous et al. reported no death in the FVP group. In contrast, one death occurred in the hydroxychloroquine group. Hassanipour et al. also showed a decrease in all-cause mortality in the FVP group compared to the control group.

The present study showed that adverse drug reactions had no differences between the two groups. However, serum creatinine was statically significant lower in the FVP group compared to the LPV/RTV group.

**TABLE 3** Clinical outcomes of the patients

|                      | FVP group (n = 32) | LPV/RTV group (n = 31) | p      |
|----------------------|--------------------|------------------------|--------|
| **Primary outcomes** |                    |                        |        |
| (day 7)              |                    |                        |        |
| SARS-CoV-2 clearance | 10 (31.3)          | 5 (16.1)               | 0.237  |
| SpO2                 | 93.0 (88.5–96.0)   | 93.0 (88.2–94.0)       | 0.628  |
| Temperature          | 36.7 (36.6–37.1)   | 37.0 (36.8–37.0)       | 0.066  |
| Respiratory rate     | 20.0 (18.0–28.5)   | 22.5 (20.0–27.5)       | 0.108  |
| **Secondary outcomes** |                  |                        |        |
| LOS in hospital, days | 6.0 (5.0–11.0)    | 8.0 (5.5–12.5)         | 0.140  |
| Admission in ICU     | 4 (12.5)           | 6 (19.4)               | 0.509  |
| In-hospital mortality|                    |                        |        |
| By Day 14            | 2 (6.3)            | 6 (19.4)               | 0.148  |
| By Day 7             | 1 (3.1)            | 1 (3.2)                | 0.999  |

Note: Values were expressed as median (IQR) or n (%). Comparison between groups was performed using the Mann–Whitney U-test or the Fisher’s exact test. Data were collected after 7 or 14 days of randomization. Abbreviations: FVP, favipiravir; LOS, length of stay; LPV/RTV, lopinavir/ritonavir, SpO2, peripheral capillary oxygen saturation.

**TABLE 4** Adverse drug reactions of the patient with confirmed COVID-19

|                      | FVP group (n = 32) | LPV/RTV group (n = 32) | p      |
|----------------------|--------------------|------------------------|--------|
| Any                  | 8 (25.0)           | 10 (32.3)              | 0.585  |
| Gastrointestinal disorders | 4 (12.5)       | 4 (12.9)               | 0.999  |
| Abnormal liver function tests | 0 (0.0)  | 1 (3.1)                | 0.999  |
| Blood pressure increase | 0 (0.0)          | 0 (0.0)                | 0.999  |
| Bradycardia          | 1 (3.1)            | 0 (0.0)                | 0.999  |
| Serum creatinine elevation | 0 (0.0)  | 2 (7.1)                | 0.214  |
| Leukopenia           | 4 (16.0)           | 3 (10.0)               | 0.689  |
| Hematuria            | 0 (0.0)            | 0 (0.0)                | 0.999  |
| Rash                 | 0 (0.0)            | 0 (0.0)                | 0.999  |

Note: Values were expressed as n (%). Data were collected within 7 days of randomization. Comparison between groups was performed using Fisher’s exact test.

Shrestha et al. also showed that noninvasive mechanical ventilation and requiring oxygen therapy was less in the patients receiving FVP.
group. Other side effects had no differences between the two groups. In contrast, Cai et al. found that more adverse events occurred in the LPV/RTV arm than those in the FVP arm. Khamis et al. showed that patients treated with FVP significantly had no side effects. Erdem et al. showed that adverse events occurred in 13% of patients treated with FVP. The most common adverse events include elevation of uric acid, total bilirubin, and liver enzymes, as well as gastrointestinal reactions. This trial includes five patients, and all of them experienced mild to moderate liver enzyme elevation. Nausea occurred in three patients, and neutropenia in one patient. All adverse events were self-limited. There was no association between serious side effects and underlying disease. Pilkington et al. found that intervention with FVP had no serious adverse events. However, hyperuricemia is a concern, and studies showed that an increase in the biochemical parameter is dose-dependent. Other complications, including QTc prolongation and teratogenic potential, have not been sufficient studies.

Considering the importance of this pandemic and treating patients with COVID-19, more studies are recommended on the role of FVP and its side effects in the management of patients with COVID-19.

4.1 Limitations

This study has several limitations. First, there is no high-effective clinically proven drug for COVID-19 to serve as a control group. Second, observation time was limited because of the urgency of this pandemic. Third, the relationship between clinical prognosis and the viral titer was not well clarified.

5 CONCLUSION

FVP may have no significant effect on mortality in patients with mild to moderate COVID-19. We should consider that the use of FVP and other antiviral drugs once the patient has symptoms may be too late, and it would explain their low efficacy. More studies with a larger sample size are recommended to evaluate the efficacy and safety of FVP.

AUTHOR CONTRIBUTIONS

Mohammad Fathalipour and Mehdi Hassaniazad developed the study design. Mehdi Hassaniazad, Hossein Farshidi, Abdollah Gharibzadeh, and Ali Bazram collected and analyzed the data and drafted the primary version of the manuscript. Mehdi Hassaniazad and Ali Bazram participated as clinical advisors of the study and included patients. Mohammad Fathalipour, Elham Khalili, and Afsaneh Noormandi participated in investigation and methodology. Mohammad Fathalipour participated in funding and supervised the trial. All authors edited and approved the final manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its Supporting Information file. Other data requests will be considered by the management group upon written request to the corresponding authors.

ORCID

Elham Khalili http://orcid.org/0000-0001-8354-9426
Mohammad Fathalipour http://orcid.org/0000-0002-4568-7024

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SUPPORTING INFORMATION
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