International Journal of Scientific Research in Dental and Medical Sciences

www.ijsrdms.com

Evaluating the Treatment with Favipiravir in Patients Infected by COVID-19: A Systematic Review and Meta-analysis

Fu Fu Wei[a,*], Azadeh Moradkhani[b], Hedieh Hemmati Hezaveh[c], Seyedeh Atefeh Miraboutalebi[d], Lida Salehi[e]

[a] *School of Medicine, Capital Medical University, Beijing, China*
[b] *Department of Internal Medicine, School of Medicine, Shahid Mohammadi Hospital, Hormozgan University of Medical Sciences, Bandar Abbas, Iran*
[c] *Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran*
[d] *School of Medicine, Guilan University of Medical Sciences, Rasht, Iran*
[e] *Department of Internal Medicine, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Article history:
Received 04 May 2020
Received in revised form 25 July 2020
Accepted 05 August 2020
Available online 12 August 2020

Keywords:
COVID-19 drug treatment
Favipiravir
SARS-CoV-2

ABSTRACT

Background and aim: Considering the results of studies and the potential of using favipiravir treatment of COVID-19, reviewing the results of clinical trial studies and summarizing the results are of great importance. It may be possible to use favipiravir extensively in the future. Therefore, the purpose of the present systematic review and meta-analysis was to evaluate the improvement rates of favipiravir treatment in patients with COVID-19.

Materials and methods: From the electronic databases, PubMed, Cochrane Library, Embase, ISI have been used to perform systematic literature between 2010 and 2020. Therefore, a software program (Endnote X8) has been utilized for managing electronic titles. Searches were performed with mesh terms. The odds ratio between the two groups (Favipiravir and control) with a 95% confidence interval was calculated. Random effects were used to deal with potential heterogeneity, and I2 showed heterogeneity. The Meta-analysis and forest plots have been evaluated using a software program available in the market (i.e., Comprehensive Meta-Analysis Stata V16).

Results: According to the research design, 186 potentially important research abstracts and titles have been discovered in our electronic searches. Finally, two papers remained in agreement with our inclusion criteria required. Statistically, a significant difference observed between improvement rates of the Favipiravir group and control group (p=0.01).

Conclusion: Positive effect and improvement rates of favipiravir VS control groups observed to treat patients with COVID-19.

1. Introduction

Since the advent of COVID-19 in Wuhan, China, in December 2019[1] the virus has spread rapidly throughout China and many other countries and is still applying.[1] Early studies reported transmitted from animals to humans, but studies have illustrated human-to-human transmission of the COVID-19 through droplets or direct contact.[2, 3] So far, the 2019-nCoV has affected more than 14,508,892 total confirmed cases (total deaths, 606,206 cases) according to a new report in global statistics of COVID-19 by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (July 20, 2020).[4] It has been reported that the asymptomatic incubation period of the virus is between 2 and 14 days. However, in some studies, the incubation period has been reported to be up to 24 days.[5] Fever, tiredness, dry cough, and shortness of breath are the most common symptoms of COVID-19. Less common symptoms are aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, a rash on the skin, or discoloration of fingers or toes.[6] .More than 80% of patients showed mild symptoms that may not increase the number of undiagnosed cases; these people are called carriers.[7] If the hospital is aggravated, it can lead to pneumonia, kidney failure, and even death. According to the WHO report, the case fatality ratio (CFR) is estimated to be over 4.5%. A cough or sneezing by a carrier can spread SARS-CoV-2 within a radius of about 6 ft. So social distance is said to minimize the spread of the disease in the community.[8] Due to the high prevalence of COVID-19 and its mortality rate, its treatment is limited, and new treatment options need to be provided. Still, due to little evidence in this field, treatment options should be developed over time. The use of existing drugs can provide an immediate treatment opportunity.[9] However, researchers now trying globally used drugs for the treatment of COVID-19, such as antimalarial hydroxychloroquine, antiretrovirals

* *Corresponding author. Fu Fu Wei*
E-mail address: 2577301219@qq.com
School of Medicine, Capital Medical University, Beijing, China
http://doi.org/10.30485/IJSRDMS.2020.241494.1079

lopinavir/ritonavir and darunavir/ritonavir, and influenza drugs oseltamivir, remdesivir, and favipiravir.[10, 11] To date, none of the treatments for COVID-19 have been definitively approved. Studies have shown that one of these treatment options that may be effective in treating COVID-19 is RNA polymerase inhibitor favipiravir, which is designed to treat influenza, Ebola, and other diseases.[12] Another study also confirmed that favipiravir leads to a significantly faster recovery rate in patients with COVID-19.[13] Considering the results of studies and the potential of using favipiravir in the treatment of COVID-19, reviewing the results of clinical trial studies and summarizing the results is of great importance. It may be possible to use favipiravir extensively in the future. Therefore, the purpose of the present systematic review and meta-analysis was to evaluate the improvement rates of favipiravir treatment in patients with COVID-19.

2. Materials and methods

Search strategy

From the electronic databases, PubMed, Cochrane Library, Embase, ISI have been used to perform systematic literature between 2010 and 2020. Therefore, a software program (Endnote X8) has been utilized for managing electronic titles. Searches were performed with mesh terms: ((("favipiravir" [Supplementary Concept]) AND (“COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] OR “COVID-19 drug treatment" [Supplementary Concept])) AND "Safety"[Mesh]) OR "Contraceptive Effectiveness"[Mesh].

This systematic review has been conducted based on the key consideration of the PRISMA[14] and PICO or PECO strategy (Table1).

Selection criteria

Inclusion criteria

1. Randomized controlled trials studies, controlled clinical trials, and prospective and retrospective cohort studies, Open-Label Control Studies.
2. Treatment of Favipiravir.
3. Success rate/ failure rate/ survival rate.
4. Patients with COVID-19.
6. No country or language restrictions.

Exclusion criteria

1. In vitro studies, case studies, case reports, and reviews.

Table 1. PICO OR PECO strategy.

PICO OR PECO strategy	Description
P	Population/ Patient: Patients with COVID-19
E	Exposure/ Intervention: Favipiravir treatment
C	Comparison: Favipiravir vs. control group
O	Outcome: success rate and safety of clinical of Favipiravir

Data Extraction and method of analysis

The data have been extracted from the research included regarding the study, years, study design, Favipiravir, control group, mean/ range of age and Onset symptoms. The quality of the studies included was assessed using the Cochrane Collaboration's tool.[15] The scale scores for low risk were 1 and for High and unclear risk was 0. Scale scores range from 0 to 6. A higher score means higher quality. For Data extraction, two reviewers blind and independently extracted data from the abstract and full text of studies included.

Moreover, the Odds ratio between two groups (Favipiravir and control) with a 95% confidence interval (CI), fixed-effect model, and Mantel-Haenszel method were calculated. Random effects were used to deal with potential heterogeneity, and I2 showed heterogeneity. The Meta-analysis and forest plots have been evaluated using a software program available in the market (i.e., Comprehensive Meta-Analysis Stata V16).

3. Results

According to the research design, 186 potentially important research abstracts and titles have been discovered in our electronic searches. In the first phase of the study selection, 156 research has been about the topics and abstracts. Therefore, we thoroughly assessed the complete full-text papers of the rest 28 studies in the second stage to exclude 26 publications due to the lack of the defined inclusion criteria. Then, TWO papers remained in agreement with our inclusion criteria required (Figure 1). Table 2 reports the individual studies in this meta-analysis.

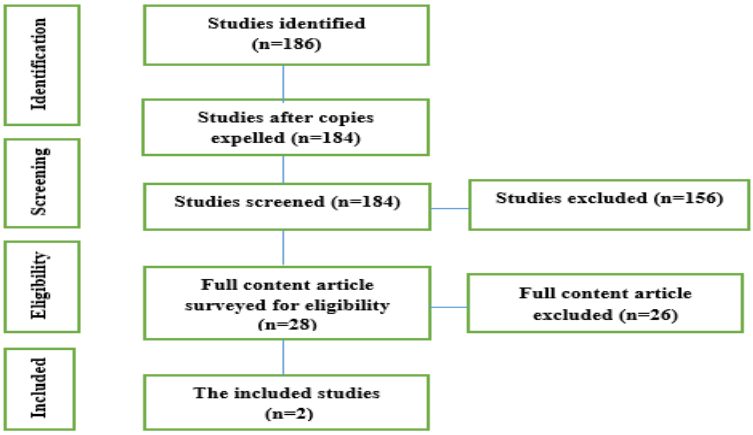

Figure 1. Study Attrition.

Sample size

Therefore, two studies (Randomized controlled trial) have been included. The Number of Patients in the Favipiravir group was 73 male and 78 female, 151 Patients with COVID-19. In the control group were 72 males and 93 females, a total of 165. The mean age in the Favipiravir group and control group was 45 years (Table 2).

Onset symptoms

All the baseline characteristics such as Fever, Cough, Headache, myalgia, Chill, Diarrhea and sore throat in Favipiravir group and control group report in table 3.

Improvement rates

The odds ratio of clinical recovery rate was 0.63 (OR 0.63 CI95% 0.16, 1.10 P=0.01) among 2 RCT studies and heterogeneity found (I2 = 76.05%; P =0.04). This result showed a statistically significant difference between the Favipiravir group and control group (p=0.01) (Figure 2).

Bias assessment

According to Cochrane Collaboration's tool, two studies had a total score of 5/6. This outcome showed a low risk of bias in all studies and high-quality assessment (Table 4).

Table 2. Studies were selected for systematic review and meta-analysis.

Study. Year	Design	Number of Patients				Mean/ Range of age		Favipiravir	Control group
		FPV		C		FPV	C		
		M	F	M	F				
Cai et al. 2020 [16]	CT	80				43 (35.5–59)	49 (36–61)	Favipiravir : Dose: 1600 mg twice daily on Day 1 Dose: 600 mg twice daily on Days 2–14	Lopinavir/ ritonavir: The dose of Lopinavir: 400 mg The dose of ritonavir: 100 mg twice daily
		35		45					
		14	21	21	24				
Chen et al. 2020 [13]	RCT	236				47	41	Favipiravir : Dose: 1600 mg twice daily on Day 1 Dose: 600 mg twice a day on Days 2–14	Arbidol Dose: 200 mg Three times daily on Day 1 -14
		116		120					
		59	57	51	69				

FPV: Favipiravir. M: male. F: female. C: control.

Table 3. Baseline Onset symptoms.

R	Onset symptoms											
	Fever		Cough		Headache/myalgia		Chill		Diarrhea		Stuffy nose/sore throat	
	FPV	C	FPV	C	FPV	C	FPV	C	FPV	C	FPV	C
[16]	22 (62.9%)	37 (82.2%)	12 (34.3%)	10 (22.2%)	3 (8.6%)	5 (11.1%)	0 (0%)	1 (2.2%)	1 (2.9%)	0 (0%)	6 (17.1%)	2 (4.4%)
[13]	64 (55.17)	61 (50.83)	70 (60.34)	64 (53.33)	2 (1.72)	3 (2.50)	NA	NA	22 (18.97)	15 (12.50)	9 (7.76)	17 (14.17)

R: references. FPV: Favipiravir. C: control.

Table 4. Risk of bias according to Cochrane Collaboration's tool.

Study. Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Total score
Cai et al. 2020 (16)	+	+	+	+	+	?	5
Chen et al. 2020 (13)	+	+	+	+	+	?	5

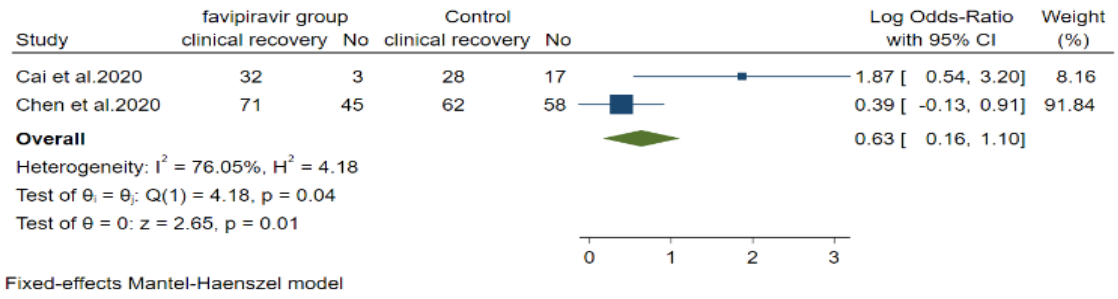

Figure 2. The odds ratio of Improvement rates between the experimental group (Favipiravir) and control group (comparison).

4. Discussion

Favipiravir (brand name: Avigan) is a drug developed by FUJIFILM Toyama Chemical Co., Ltd. (Japan). In 2014, it was reported by Fujifilm Toyama Chemical to neuraminidase inhibitors and treatment of influenza.[17] Favipiravir has also been used to treat infections caused by RNA viruses such as Ebola, norovirus, and influenza.[18] Recent studies have shown that favipiravir can be used to treatment of SARS-CoV-2 that is a single-stranded RNA virus. An in vitro study reported ribavirin, favipiravir, penciclovir, nafamostat, remdesivir, nitazoxanide, chloroquine are anti-SARS-CoV-2 medicines.[19] Clinical trial studies have shown that patients' treatment with favipiravir showed a superior improvement rate (71.43%) than patients' treatment with umifenovir.[13] Based on repeated findings and searches, eight studies have been performed to evaluate the effect of favipiravir aniSARS-CoV-2. These studies include the evaluation of non- randomized and randomized controlled trials. In the present meta-analysis, only two clinical trials[13, 16] were included, a control group to compare the experimental group. The present systematic review and Meta-analysis findings show favipiravir have high Improvement rates VS other medicines. Wu et al.[20] in an updated review of drugs treating COVID-19, reported favipiravir to treatment COVID-19. Also, Arab-Zozani et al.[21] determine the safety and effectiveness of favipiravir treatment of coronavirus. In this study, No RCT studies have been reported, no meta-analysis of results has been reported, and no comprehensive results have been reported. Another review by ilkington et al.[10] determined favipiravir's safety; the result reported that favipiravir showed a favorable safety profile. Evidence suggests that the short-term use of favipiravir showed safety and tolerability. According to the findings, the use of favipiravir seems to be an effective treatment of COVID-19. However, to confirm these outcomes, more RCT studies with a high sample size and follow-up period are needed.

5. Conclusion

The present study shows a positive effect of favipiravir VS control groups to treat patients with COVID-19. Favipiravir is currently conducting clinical trials to evaluate its effectiveness and Immunity treatment of COVID-19. To achieve a more accurate outcome. It is hoped that the present study results can help assess the clinical recovery and efficacy of Favipiravir to treat patients with COVID-19 vs. other drugs and physicians selecting better treatment.

Conflict of Interest

The authors declared that there is no conflict of interest.

Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

[1] Schwartz DA, Graham AL. Potential maternal and infant outcomes from (Wuhan) coronavirus 2019-nCoV infecting pregnant women: lessons from SARS, MERS, and other human coronavirus infections. Viruses. 2020;12(2):194. https://doi.org/10.3390/v12020194.

[2] Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment coronavirus (COVID-19). InStatpearls [internet] 2020. StatPearls Publishing.

[3] Borges do Nascimento IJ, Cacic N, Abdulazeem HM, von Groote TC, Jayarajah U, Weerasekara I, Esfahani MA, Civile VT, Marusic A, Jeroncic A, Carvas Junior N. Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. Journal of clinical medicine. 2020;9(4):941. https://doi.org/10.3390/jcm9040941.

[4] (CSSE) CfSSaE. global statistics of COVID-19 2020.

[5] Li H, Liu Z, Ge J. Scientific research progress of COVID‐19/SARS‐CoV‐2 in the first five months. Journal of cellular and molecular medicine. 2020;24(12): 6558-70. https://doi.org/10.1111/jcmm.15364.

[6] Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, Iosifidis C, Agha R. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). International Journal of Surgery. 2020;76:71-76. https://doi.org/10.1016/j.ijsu.2020.02.034.

[7] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. Jama. 2020;323(13):1239-42. doi:10.1001/jama.2020.2648.

[8] Ather A, Patel B, Ruparel NB, Diogenes A, Hargreaves KM. Coronavirus disease 19 (COVID-19): implications for clinical dental care. Journal of endodontics. 2020;46(5):584-95. https://doi.org/10.1016/j.joen.2020.03.008.

[9] Kalil AC. Treating COVID-19—off-label drug use, compassionate use, and randomized clinical trials during pandemics. Jama. 2020;323(19):1897-8. doi:10.1001/jama.2020.4742.

[10] Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir–a potential treatment in the COVID-19 pandemic?. Journal of Virus Eradication. 2020;6(2):45.

[11] Mitjà O, Clotet B. Use of antiviral drugs to reduce COVID-19 transmission. The Lancet Global Health. 2020;8(5):e639-40. https://doi.org/10.1016/S2214-109X(20)30114-5.

[12] Xuan Y. Initial clinical results announced for favipiravir treatment of novel coronavirus pneumonia-viral clearance in four days. Biodiscover. 2020.

[13] Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, Chen B, Lu M, Luo Y, Zhang J, Yin P. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv. 2020.

[14] Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, Atkins D, Barbour V, Barrowman N, Berlin JA, Clark J. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement (Chinese edition). Journal of Chinese Integrative Medicine. 2009;7(9):889-96. 10.3736/jcim20090918.

[15] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928.

[16] Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, Liao X, Gu Y, Cai Q, Yang Y, Shen C. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering. 2020. https://doi.org/10.1016/j.eng.2020.03.007.

[17] Kikuchi G, Motokawa Y, Yoshida T, Hiraga K. Glycine cleavage system: reaction mechanism, physiological significance, and hyperglycinemia. Proceedings of the Japan Academy, Series B. 2008;84(7):246-63. https://doi.org/10.2183/pjab.84.246.

[18] De Clercq E. New nucleoside analogues for the treatment of hemorrhagic fever virus infections. Chemistry–An Asian Journal. 2019;14(22):3962-8. https://doi.org/10.1002/asia.201900841.

[19] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell research. 2020;30(3):269-71. https://doi.org/10.1038/s41422-020-0282-0.

[20] Wu R, Wang L, Kuo HC, Shannar A, Peter R, Chou PJ, Li S, Hudlikar R, Liu X, Liu Z, Poiani GJ. An update on current therapeutic drugs treating COVID-19. Current Pharmacology Reports. 2020;6:56–70. https://doi.org/10.1007/s40495-020-00216-7.

[21] Arab-Zozani M, Hassanipour S, GHoddoosi-Nejad D. Favipiravir for treating novel coronavirus (COVID-19) patients: protocol for a systematic review and meta-analysis of controlled trials. medRxiv. 2020.

How to cite this Article: Wei F, Moradkhani A, Hemmati Hezaveh H, Mirabootalebi S, Salehi L. Evaluating the Treatment with Favipiravir in Patients Infected by COVID-19: A Systematic Review and Meta-analysis. International Journal of Scientific Research in Dental and Medical Sciences, 2020;2(3): 87-91. doi:10.30485/IJSRDMS.2020.241494.1079.