JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Comparative Study of Favipiravir Plus Ivermectin and Doxycycline Versus Ivermectin and Doxycycline Therapy on Covid-19 Patients: A Retrospective Study

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Article History:

Received 28 Feb 2022
Accepted 29 March 2022
Available online 31 March 2022

Citation:
Lakhani N., Desai S., Desai C., Merai A., Paul A. A Comparative Study of Favipiravir Plus Ivermectin and Doxycycline Versus Ivermectin and Doxycycline Therapy on Covid-19 Patients: A Retrospective Study **J Pharm Sci Bioscientific Res**. 2022. 11(2): 84-87

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ABSTRACT:

Introduction: Covid-19 is a pandemic that doesn't require any further introduction as currently, the entire world is passing through a tough fight against the infection. Mortality among patients becomes more complicated to treat with available resources. Vaccines have played a tremendous role in preventing further complications. Methodology: A Retrospective, observational, comparative study to observe safety and efficacy of Fabiflu Plus Doxycycline- Ivermectin Versus Doxycycline-Ivermectin in Covid-19 Patients on an OPD basis. The sample size was 50 were 25 for each group of treatment. The study was designed to compare the effect of treatment on oxygen saturation and inflammatory markers in participants. The secondary objectives were to compare the effectiveness of the intervention on clinical parameters in participants. Results and discussion: All the participants recovered well, there were no patients who progressed towards mortality. There was a significant reduction in CRP level in a group that received favipiravir plus ivermectin and doxycycline. The oxygen saturation and haemoglobin level remain sustained in both groups. Conclusion: Both group participants had sustained oxygen saturation and no one progressed to mortality. The effect of favipiravir with ivermectin and doxycycline combination requires prospective evaluation in a larger sample size. Furthermore, consideration of the standard of care, and monitoring more laboratory parameters post completion of the study to evaluate safety and efficacy.

KEY WORDS: covid-19, Favipiravir, ivermectin, doxycycline

INTRODUCTION

Covid-19 is RNA based viral infection with many variant strains available now in the world that need no further introduction. Many anti-viral antibiotics and supplementations were investigated for the treatment of covid-19. To prevent complications and mortality in patients of covid-19 warriors have exhibited tremendous efforts to clinically tackle the situation before the arrival of vaccines.[1-3] Many attempts have been made to combat Covid-19 infection like anti-virals, anti-SARS COV-2 neutralizing antibodies, Immunomodulatory agents, anti-parasitic agents, antibiotics, and many herbal formulations.[4]SARS-CoV-2 is inhibited by ivermectin which is the anti-parasitic medicine, it prevents viral proteins from accessing the nucleus of the host cell.[5] Doxycycline was found as a possible inhibitor of SARS-CoV-2 papain-like protease in virtual pharmacological screening.[6] The fact that SARS-CoV-2 replicates rapidly in the respiratory system and that evidence from animal models shows three-fold higher levels of ivermectin in pulmonary tissue than in plasma at one week after oral medication emphasizes the need even more.[7] Favipiravir (FPV) is a new RdRp inhibitor that has shown to be effective in the treatment of influenza and Ebola virus infections.

Considering positive effect in reported case studies, and effectiveness clinical results in mild to moderated patients require further clinical evaluation regarding its effect along with ivermectin and doxycycline in covid-19 patients.[8] Finding an effective combination of medicine in covid-19 therapy is important for reducing mortality progression.

Methodology:

The study followed the ICH-GCP guideline, and the study protocol was approved by the independent ethics committee of Kasturba Hospital Valsad. It was a retrospective observational case-control study designed to evaluate the safety and efficacy of Fabiflu Plus Doxycycline-Ivermectin Versus Doxycycline-Ivermectin in Covid-19 Patients on an OPD basis. Both the groups have received standard of care along with this study medications. As it was a retrospective study no hypothesis testing was required so the sample size was not calculated based on it. Although the sample size was selected 50 covid-19 patients (25 for each group) to compare the objectives and outcomes based on criteria. Patients between 18 to 80 years old who tested positive for SARS-CoV-2 infection by Real-time polymerase chain reaction (RT-PCR) at Kasturba Hospital in Valsad from May 1 to 30 July 2020, were initially included in this study, both with and without symptoms. Only patients with an oxygen saturation of 94 percent or higher and who followed the Covid-19 outpatient therapy protocol were included in the study. Chest radiographs were taken on patients who had respiratory complaints. Participants with normal or near-normal chest radiographs (up to 10% involvement) were included in the study. All patients were given a thorough examination, which included a review of their present illness, concomitant conditions, and complaints. Patients with ischemic heart disease (IHD), asthma, chronic obstructive pulmonary disease (COPD), hepatic illness, cancer, uncontrolled diabetes mellitus (DM), and severe renal impairments were excluded. Patients who were hospitalized or immune-compromised were also excluded. The primary objective was to study the effect of interventions on oxygen saturation and inflammatory markers with endpoints baseline and 5th-day observation parameters. Secondary objectives were to study the effect of the intervention on clinical parameters with endpoints baseline and 5th-day observation parameters. The target population was male, female, and transgender. The estimated duration of the trial was 3 months. Results for significance were analysed by paired sample t-test.

Result and Discussion: Participants categorized in two groups group1 (Favipiravir+Ivermectin+Doxycyclin) and Group 2 (Ivermectin+ Doxycyclin) respectively. The enrolled study participants mean age group was 51.32 ± 14.73 and 50.12 ± 15.281(Mean ±SD) for Group 1 and Group 2.

The primary objective of the study was to assess the effect of the intervention on oxygen saturation and inflammatory markers. The results in table 1 mentioned the results of both group effects on the baseline and after the 5th day on oxygen saturation and haemoglobin level. The reason mainly the complications that arise in covid-19 might be due to oxygen saturation level decline in patients. The source of oxygen transport in the human body is haemoglobin. Therefore, both the parameters were observed for the clinical effect in both groups. Both the groups were able to sustain haemoglobin and oxygen saturation but there was no significant improvement has been observed. Clinical observation suggests sustaining oxygen saturation and haemoglobin may prevent further complications in covid-19 patients. [9] This might help prevent the progression of disease into the mortality stage.

Table 1: Effectiveness of treatment on oxygen saturation and haemoglobin level.

Table 1 Effectiveness of treatment on oxygen saturation and haemoglobin level.

Group I where n=25 Patients			
Variables	**1th day**	**5th day**	**p-value**
SpO2 (%)	96.12 ± 1.72	96.40 ± 1.12	0.464
Hb (gm/dl)	12.21 ± 2.04	12.23 ± 1.62	0.917
Group 2 where n=25 Patients			
Variables	**1th day**	**5th day**	**p-value**
SpO2 (%)	96.80 ± 1.47	96.72 ± 1.57	0.753
Hb (gm/dl)	12.17 ± 1.81	12.26 ± 1.71	0.494
Values are expressed in Mean ± SD and p-values are estimated by using paired sample t test.			

Ivermectin and Doxycycline have shown antiviral and immunomodulatory activities. [10-13] Ivermectin and Doxycycline are approved by FDA and have a supportive historical safety record. Doxycycline is a broad-spectrum antibiotic belongs to the tetracycline class which resolves the problem of secondary bacterial infection in Covid-19 patients. [14-15] There was no documented interaction between both the drugs as well as any of the medications given in the standard care.[16]

Studies have already reported the importance of inflammation in the progression of the covid-19 infection into complicated complications.[17] So, the treatment

approach also demands preventing progression of the inflammatory condition restricting lung damage, and further complications. The results mentioned in table 2 indicated that Favipiravir + ivermectin and doxycycline have a significant reduction ($p<0.05$) of CRP report. This might indicate potential anti-inflammatory action and positive reflection towards preventing the disease progression.

Table 2 Effectiveness on inflammatory markers.

Group I where n=25 Patients			
Variables	**1th day**	**5th day**	**p-value**
CRP	30.25 ± 31.81	10 .03 ± 10.60	0.003
LDH	235.40 ± 68.23	249.68 ± 179.06	0.699
Group II where n=25 Patients			
Variables	**1th day**	**5th day**	**p-value**
CRP	23.54 ± 23.20	20.26 ± 36.72	0.683
LDH	260.24 ± 111.63	259.00 ± 98.74	0.823
Values are expressed in Mean ± SD and p-values are estimated by using paired sample t test.			

Table 3 Evaluation of effectiveness of treatment on clinical parameters.

Variables, n (%)	**Group-I n=25 Patients**	**Group-II n=25 Patients**
Fever	21 (84.00)	18 (72.00)
Cough	12 (48.00)	15 (60.00)
Fatigue	15 (60.00)	16 (64.00)
Shortness of Breath	00 (00.00)	03 (12.00)
Expectoration	02 (08.00)	00 (00.00)
Myalgia	02 (08.00)	05 (20.00)
Rhinorrhoea	00 (00.00)	00 (00.00)
Sore throat	00 (00.00)	04 (16.00)
Diarrhoea	02 (08.00)	05 (20.00)
Anosmia	00 (00.00)	00 (00.00)
Ageusia	02 (08.00)	00 (00.00)
Decrease in appetite	05 (20.00)	04 (16.00)
Chills	04 (16.00)	02 (08.00)
Headache	02 (08.00)	07 (28.00)
Backache	03 (12.00)	03 (12.00)

The effect of treatment on clinical parameters in table 3 indicates that symptoms like fever; fatigue, coughing, and shortness of breathing showed remarkable improvement on the 5th day in participants. Therefore, giving Standard of care like zinc, vitamin-C, Vitamin-D, and steroids to both groups along with treatment formulations at the viral and the hyperinflammatory phase of the disease appears clinically of benefit. [18-20] This might shape the future most-fit combinational therapy of Covid-19 patients to minimize as could as possible the mortality and decrease the duration and the progression of the disease. Compared to other anti-virals favipiravir is affordable amongst all available options and may become a vital option in emergency use and prevent mortality conditions in covid-19 patients.[21] More research is already in progress to establish its untoward effects, effect in critical covid-19 patients, and possible combination approaches in covid-19 management.

Our study has limitations, it is retrospective so case selection and these include relatively small sample size. The outcome may be biased by factors like disease severity or existing co-morbidities. The inclusion of another supportive measure in the trial might also play a significant role in the recovery and prevention of mortality amongst participants. Also, the study included only Covid-19 patients who were mildly or moderately ill and therefore had a better prognosis than severely or critically ill patients.

CONCLUSION

The results suggested that the oxygen saturation remains well maintained so hypoxia-induced clinical symptoms are not progressed to complications. The addition of favipiravir along with ivermectin and doxycyclin have an observational reduction in CRP suggests reducing inflammation-mediated damage and complications. There was an observational reduction in clinical parameters in participants. Participants had not developed any further complications. The effect of favipiravir with ivermectin and doxycycline combination requires prospective evaluation in a larger sample size, consideration of the standard of care, and monitoring more laboratory parameters post completion of the study to evaluate safety and efficacy.

Conflict of Interest

The authors have no conflict of interest.

ACKNOWLEDGEMENT:

Authors express sincere thanks to Ethics committee of Kasturba Hospital, Valsad for providing support to proceed for the study.

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