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A comparative study on ivermectin- doxycycline and favipiravir therapy in COVID19 patients

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Abstract
Objectives: We investigated the outcomes of Ivermectin-Doxycycline vs. Favipiravir therapy in mild to moderate COVID19 patients.
Methods: Patients were divided randomly into two groups: Ivermectin 200µgm/kg single dose + Doxycycline 100mg BID for ten days in group A, and Favipiravir 1800mg for the first day, then 800mg BID for six days in group B (Control group). RT-PCR for SARS-CoV-2 infection was repeated in all symptomatic patients on the second day onward without symptoms. Repeat PCR was done every two days onward if the result found positive. Time to the negative PCR and symptomatic recovery was measured for each group.
Results: All subjects in Group A reached a negative PCR, at a mean of 8.93 days, and reached symptomatic recovery, at a mean of 5.93 days, with 55.10% symptom-free by the fifth day. In group B, 96.36% reached a negative PCR at a mean of 9.33 days and were symptoms-free at 6.99 days. In group a 31.67% of patients expressed symptoms caused by medication, this was 46.43% in group B.
Conclusion: The combination therapy of Ivermectin-Doxycycline showed a trend towards superiority to the combination of Favipiravir for mild to moderate COVID19 disease.

Keywords: COVID-19, doxycycline, favipiravir, ivermectin

Introduction
Coronavirus disease 2019 (COVID-19) is a global pandemic declared by the world health organization (WHO). Over ninety million people have already been infected by severe acute respiratory syndrome- coronavirus- 2 (SARS-CoV-2), and billions have been affected by the socioeconomic squeal. As SARS-CoV-2 is a novel virus, there are no proven treatment options yet. Early treatment before the disease becomes severe would be optimal. Recently, an anti-parasitic drug Ivermectin has been described as highly effective in an *in vitro* study against SARS-CoV-2 [4]. an encouraging result in a case series of COVID19 patients with a combination of Ivermectin and Doxycycline. Ivermectin is well-tolerated, less toxic, and has fewer adverse effects than Favipiravir.

Methods
Informed Consent was taken. The individuals who gave consent were enrolled in this study. Study Population and Data Collection Patients (16 years to 80 years of age) tested positive for SARS-CoV-2 infection by Real-time polymerase chain reaction (RT-PCR) at Geetanjali Medical College and Hospital from May 2020 to the December 2020, were initially included in this study, including those with and without the symptoms. All patients received a full evaluation, including a history of current illness, comorbid condition, and associated complaints. Patients with unstable comorbid conditions like bronchial asthma, chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD), uncontrolled diabetes mellitus (DM), advanced renal and hepatic disease, carcinoma, hospitalized, and immuno-compromised patients were excluded. Patients were examined for oxygen saturation and only those with oxygen saturation of 95% or above who fit the outpatient treatment protocol for COVID19 were included. Patients with respiratory symptoms received chest radiographs. Those with normal or near-normal chest radiographs (up to 10% involvement) were

included. Randomization and Treatment Intervention Randomization was done using an odd-even methodology and applied to registration number of study patient, consecutively in a 1:1 ratio. Treatment was given, and the final enrolment was done by the attending physician (investigator). All the patients enrolled in this study were treated as outpatient department (OPD) patients. For the study, patients were divided into two groups, as follows: • Group A (n=60): Ivermectin 200µgm/kg single dose + Doxycycline 100mg BID for ten days. • Group B (n=56): Favipiravir 1800mg for the first day, then 800mg BID for six days. All the subjects were provided with symptomatic treatment such as fever, headache, cough, and myalgia. Drug interactions and contraindications for each individual were considered carefully. The schedule of medication intake was adequately explained to each patient. Group A's instructions included that Ivermectin tablet (200µg/ kg) single dose to be taken on an empty stomach an hour before a meal on the first day. Doxycycline 100 mg capsule be taken twice daily after meal for ten days starting from day one. Group B's instructions included Favipiravir 1800mg for the first day, then 800mg twice daily after meal for six days. Patients were advised to self-isolate, take proper nutrition, hydration, and maintain a sanitary environment. Repeat Nasopharyngeal and Throat Swab PCR All subjects underwent repeat nasopharyngeal and throat swab PCR for SARS-CoV2 every other day until their PCR was negative. These repeat PCR tests began on the fifth day after taking the medication for subjects who began the study and remained symptom-free. The PCR repeat testing began on the second symptom-free day onward for subjects who began the study with symptoms or developed symptoms. The investigators had telephone contact with all the subjects every three days throughout the study to determine any therapy's adverse effects. A re-evaluation PCR was performed after seven days following the first negative PCR.

Data Analysis and Statistics: Data were presented as mean±standard deviation, and statistical analysis was done by Graph pad Prism software. Column analysis was done to find the mean with the standard deviation in each group. T-test was done to see the significance between the values where needed. P>0.05 was considered statistically significant.

Results

181 patients tested positive for SARS-CoV-2 infection in that period. 42 patients had comorbid conditions (some required hospitalization) that might have affected the recovery time, and 14 patients were unwilling to participate in the study. Nonetheless, 9 patients did not show-up (3 from group A and 6 from group B) for the follow-up sample collection, so these were excluded, and 116 patients were finally included in the analysis. Demographic Characteristics of the Study Subjects As shown in Table 1, the total number of patients was 116; male 84 and female 26, age 16 to 80 years, and mean age (33.94±14.12 years). Group A (Ivermectin + Doxycycline): male 43 (71.67%), female 17 (28.33%), age 35.72±15.1 years; males 37 years and female 32.88 years. Group B (Favipiravir): male 47 (83.93%), female 9 (16.07%), age 31.91 years; male 31.35, and female 34.5 years. Among the total, 91 (78.45%) were symptomatic, and 25 (21.55%) were asymptomatic patients with contact history. These were 49 (81.67%) and 11 (18.33%) in group A, 42 (75%) and 14 (25%) in group B. Recovery Rate and Mean Recovery Duration Between Groups In group A, recovery to negative PCR rate was 100% (60/60). The mean recovery duration to negative PCR was 8.93 days (8 to 13 days). 41 (63.3%) of patients had no new complaints other than their presenting symptoms. New symptoms that may have been attributed to adverse drug effects included lethargy in 14 (23.3%), nausea in 11 (18.3%), and occasional vertigo in 7 (11.66%) of patients (Fig. 1c). In group B, out of 56 patients, two male patients were shifted to ICU. They did not recover to a negative PCR as part of the study. Therefore, the recovery rate to negative PCR was 96.36% (54/56). The mean duration of recovery to negative PCR was 9.33 days (5 to 15 days). 30 (53.57%) of the patients had no new complaints other than their presenting symptoms. Fresh symptoms that were recognized as an adverse effect of HCQ included 13(23.21%) with mild blurred vision and headache; 22 (39.2%) with increased lethargy and dizziness, 10 (17.85%) with occasional, mild palpitation, and 9 (16.07%) with nausea and vomiting. Difference in Recovery to Negative PCR between Groups The difference between group A and group B recovery to negative PCR duration was not statistically significant in unpaired t-test, p=0.2314. Subgroup analysis of the recovery duration: male 9.18±1.90 days and female 8.92±1.32 days, p=0.515; in group A male 8.907±1.342 days and female 9±1.173 days, p=0.44; and in group B male 9.18±1.90 days and female 8.92±1.32 days, p=0.407. The recovery duration of both group males and females were not significant, p=0.18 and 0.69, respectively. The mean duration of symptomatic recovery was 5.93 days (5 to 10 days) in group A and 6.99 days (4 to 12 days) in group B. This difference in time to symptomatic recovery between group A and group B is not statistically significant, p=0.071. In group A, over half of the subjects had become symptom-free by five days 27 (55.10%), with the remaining subjects becoming symptom-free on day six (16.32%), day seven (12.24%), day eight (8.16%), day nine (4%), and day ten (2.04%). In group B, recovery was slower with subjects becoming symptoms free on fourth day 3 (7.14%), the fifth day 10 (23.8%), sixth day 9 (21.43%), seventh day 8(19.04%), eighth & ninth day 4 (9.52% each), eleventh day 2 (4.76%), and tenth and twelfth day (2.38% each). Mean Duration of Time to Negative PCR between Groups In the secondary analysis of subjects who began the study with symptoms, the mean duration of time to negative PCR was 9.061 days in group A and 9.738 days in group B. This was not statistically significant in the unpaired t-test, p=0.0714. The mean duration of time to becoming negative PCR of patients without symptoms was 8.364 days in group A and 7.917 days in group B, which was not statistically significant in unpaired t-test, p=0.443. Further analysis showed the highest recovery was achieved on the eighth day among group A patients in case of both asymptomatic (n=11) and symptomatic (n=49) patients, 8 (72.72%) and 22 (44.89%), respectively (Fig. 2 c, d). This recovery was relatively slower in group B. On the sixth day 3 (7.5%), seventh day 1 (2.5%), eighth day 9 (22.5%), ninth and tenth day 8 (20%) each, eleventh and twelfth day 4 (10%) each, thirteenth day 1 (2.5%), and fourteenth day 2 (5%) in group B patients with symptoms (n=40). Among asymptomatic patients (n=14), this was 1 (7.5%) on the fifth day, 2 (14.2%) individually on the sixth, seventh, eighth, tenth day, 4 (28.57%) on the ninth day, and 1 (7.1%) on the eleventh

day. No significant difference in the recovery duration was found in the subgroup analysis of the recovery duration according to the study group's age. 61 to 70 years in group A had the longest recovery duration, 9.5±2.12, and 71 to 80 years was the shortest 8 days. In group B, this was 11.71±2.48 days in the 41 to 50 years and 8.37±2.44 days in the 10 to 20 years age group.

Table 1: Baseline characteristics of the study group patients.

Parameters	
Number of patients (n)	116
Male	90
Female	26
Group A (n)	60
Group A Male	43
Group A Female	17
Group B (n)	56
Group B Male	47
Group B Female	9
Age (in years)	33.94±14.12 (8 to 80 Years)
Symptomatic	91 (78.45)
Asymptomatic (n, %)	25 (21.55)

Table 2: Showing Group A

Age group A (in years)	35.72±15.1
Male	37
Female	32
Symptomatic	49
Asymptomatic	11

Table 3: Showing Group B

Age group B (in years)	31.91±12.72
Male	31
Female	34
Symptomatic	42
Asymptomatic	14

Discussion

The COVID-19 pandemic in India is part of the coronavirus worldwide pandemic disease caused by a newly discovered coronavirus. It was initially called novel coronavirus and later named SARS-CoV-2 due to its similar characteristics with SARS-CoV-1 [7-9]. New concerns about Favipiravir has led us to seek alternatives with shorter recovery time and better tolerability. Thus, we have undertaken a comparative therapeutic analysis, comparing these standard drugs with Ivermectin and Doxycycline. In this treatment study of groups A and B, the presenting symptoms of the COVID19 patients were fever, cough, sore throat, weakness, chest discomfort, breathing difficulty, diarrhea, myalgia, and abdominal pain. To avoid the recovery duration's influence, we solely selected the cases devoid of severe comorbidities. The difference in recovery to negative PCR duration was not significant (p=0.231) among the two groups. The mean recovery duration is shorter, 8.933 days in group A than in group B, 9.33 days. Also, group A had a better outcome ratio of 100% (60/60) recovery to negative PCR compared to that of group B 96.36% (54/56). At present, it has been the topic of discussion concerning Favipiravir potential use to treat patients with COVID-19 [11]. It is thought that the effect of Favipiravir results in the selective killing of the infected cells. Therefore, it may accelerate viral clearance in COVID-19 [13]. Some studies showed that severe deterioration in some patients with COVID-19 had been closely associated with dysregulated and excessive cytokine release termed "cytokine storm [14, 15]." Favipiravir was found to inhibit SARS-CoV-2 infection *in vitro* and significantly decrease cytokine production, especially the pro-inflammatory cytokines [16]. On the other hand, Ivermectin is a relatively safe and well-tolerated anti-parasitic drug that can inhibit nuclear transport activity [20]. Recently, *in-vitro* studies have shown its function against SARS-CoV-2 [21, 22]. A report suggested that Ivermectin reduces mortality rates in hospitalized patients with COVID-19 [23]. However, it is unknown if antiviral levels are attainable while using known dosing regimens of Ivermectin therapy in patients with COVID-19. [24, 25] Thus, it is vital to investigate Ivermectin's dose regimens for COVID-19 treatment or to determine if there is appropriate synergism using combination therapy with another drug. Also, Doxycycline is a tetracycline class of antibiotics with a long history of clinical use [26]. The efficacy and tolerability of Ivermectin and Doxycycline were established in combination with an earlier study to treat onchocerciasis [27]. Several recent studies have suggested a therapeutic role of Doxycycline against COVID-19 [28, 29]. In our study, the difference in recovery to become symptom-free was not statistically significant. Nevertheless, the Ivermectin group showed better symptomatic recovery than the Favipiravir group. According to the age among study groups, the difference was not statistically significant. Ivermectin-Doxycycline combination expressed an earlier and faster relief of COVID features and viral clearance than the favipiravir combination. However, the mean recovery duration is not statistically significant. In the Ivermectin-Doxycycline group a greater number of patients gained faster symptomatic recovery than that of the Favipiravir group. This suggests Ivermectin-Doxycycline may have better efficacy in reducing the COVID-19 symptoms than Favipiravir therapy. The Ivermectin-Doxycycline group had better patient compliance and fewer adverse effects compared to the Favipiravir group. The adverse effects of Favipiravir in our study are similar to others [30, 31]. The sex difference was also examined, but there were no significant differences between males and females in this study. According to this study, the Ivermectin-Doxycycline treatment regimen was well tolerated, and effective treatment for mild to moderate degrees of SARS-CoV-2 infection. Not only concerning the time to become symptom-free and the viral clearance, but also in terms of safety, side-effect profile, and compliance the Ivermectin-Doxycycline combination is superior to Favipiravir therapy for mild to moderate degrees of COVID-19 patients. We strongly believe that increasing the dose and the duration of Ivermectin treatment will further benefit in reducing the recovery period of COVID19 infection beyond that which was seen in our study. This will also prevent disease progression and morbidity in COVID-19 patients. Our study has limitations, and these include relatively small sample size, the dose of Ivermectin, and case selection. The outcome may be biased by factors like disease severity, lack of cooperation of some participants, and unknown comorbidity.

Conclusion

According to our study, the Ivermectin-Doxycycline combination therapy has better symptomatic relief, shortened recovery duration, fewer adverse effects, and

superior patient compliance compared to the Favipiravir. Based on this study's outcomes, the Ivermectin-Doxycycline combination is a superior choice for treating patients with mild to moderate COVID-19 disease. Despite this study's limitation, we tried to select our study group patients without any major or unstable comorbid condition as far as possible to avoid differences in treatment outcomes among the groups.

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