Research Article
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Comparison of the intensive care unit admission rate and mortalities of COVID-19 patients who received Hydroxychloroquine and Favipiravir in the ward

Abstract

Background: Until now, a fully accepted treatment method for the management of COVID-19 has not been recommended. Some antiviral drugs such favipiravir and remdesivir, antimalarial drugs like hydroxychloroquine and anti-inflammatory drugs have been used for the treatment of the patients with COVID-19. The aim of this retrospective study is to compare the Intensive Care Unit (ICU) admission rate and mortalities of COVID-19 patients who received Hydroxychloroquine and Favipiravir in the COVID positive wards.

Methods: First approval was obtained from the ethics committee, then the patients with COVID-19 who were under follow-up and treat in the COVID positive wards between March and December 2020 were retrospectively analyzed. We aimed to investigate the demographic characteristics, the reason for hospitalization, Charlson comorbidity index, hemodynamic and laboratory parameters, duration of the ward, the rate of discharged from the ward, the ward mortality rate, the ICU admission rate, and mortalities of these patients. The patients were divided into two groups as Hydroxychloroquine Group (H Group) and Favipiravir Group (F Group). The patients in the H Group received hydroxychloroquine 400 mg orally 2x/day on day 1, then 200 mg 2x/day on days 2-5. The patients in the F group received favipiravir 1600 mg 2x/day on day 1, then 600 mg 2x/day on days 2-5. Decreased oxygen saturation and PaO2/FiO2 rate, increased respiration rate with worsening clinical condition and elevated inflammatory parameters such CRP, ferritin, D-dimer, creatinine, lactate and troponin were accepted as criteria for admission to ICU. Demographic and clinical characteristics, and the ICU admission rate, the discharge from the ward and mortalities were compared between the two groups.

Results: A total of 2734 patients were analyzed retrospectively and divided into H and F groups. The main reasons for hospitalization were fatigue, shortness of breath, fever, low oxygen saturation and positive PCR test with positive chest computerized tomography findings for COVID-19 in all patients. Age, gender, Body Mass Index (BMI), Charlson Comorbidity Index (CCI), mean blood pressure, heart rate, respiratory rate and oxygen saturation were not significant different between the H and F groups at admission.

The treatments of the patients in the wards such the support of oxygen with reservoir mask, enoxaparin as an anticoagulant, acetylcysteine to loss mucus in the airways, steroid use, vitamin C and D, and patient's nutrition were the same. The ICU admission criteria were similar between the two groups.

The rate of discharged from the ward was significantly higher in the H group when compared with F group as 85,75% versus 73,74%. In addition, the ICU admission rate was significantly lower in the H group than F group as 9,79% versus 20,54%.

The ward mortality and ICU mortality rates were not significant different between the two groups. However, total mortality rate, considering of the total ward and ICU, was significantly lower in The H group.

Conclusion: This retrospective study showed that hydroxychloroquine lowers the ICU admission rate and raises the discharge rate when compared with favipiravir in the ward patients with COVID-19. However, it does not change the ward and the ICU mortality rates.

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Introduction

A specific treatment has not yet been registered for COVID-19 to date, which the World Health Organization officially declared as a global pandemic on March 11, 2020. Some antiviral drugs such favipiravir[1] and remdesivir,[2] antimalarial drugs like hydroxychloroquine[3] and anti-inflammatory drugs[4,5] have been used for the treatment of the patients with COVID-19. A recently published review article lists recommended therapeutic approaches for COVID-19 from one to ten as follows: isolation, oxygen support, respiratory treatment, anticoagulant treatment, anti-inflammatory drugs, hydroxychloroquine and combinations therapies, antiviral drugs, convalescent plasma therapy, mesenchymal stem cells therapy and vaccination.[6]

Although it is an antimalarial drug, hydroxychloroquine was used in the early period in the treatment of COVID-19 patients due to its immunosuppressive effect and low cost.[7,8] Favipiravir exerts its antiviral effect by inhibiting RNA polymerase and preventing viral transcription. It has been reported that when Favipiravir is used in the early period, it can improve clinical outcomes with its antiviral effect in COVID-19 patients.[9]

The aim of this retrospective study is to compare the Intensive Care Unit (ICU) admission rate and mortalities of COVID-19 patients who received Hydroxychloroquine and Favipiravir in the COVID positive wards.

Materials and methods

First approval was obtained from the ethics committee, then the patients with COVID-19 who were under follow-up and treat in the COVID positive wards between March and December 2020 were retrospectively analyzed. A total of 2734 patient were investigated in this retrospective study. It was planned to investigate the demographic characteristics, the reason for hospitalization, Charlson comorbidity index, hemodynamic and laboratory parameters, duration of the ward, the rate of discharged from the ward, the ward mortality rate, side effects such QT interval prolongations, AST and ALT elevations, and then the ICU admission rate, the ICU mortalities and total mortalities of these patients.

The patients were initially divided into two groups as Hydroxychloroquine Group (H Group) and Favipiravir Group (F Group). The patients in the H Group received hydroxychloroquine 400 mg orally 2x/day on day 1, then 200 mg 2x/day on days 2-5. The patients in the F group received favipiravir 1600 mg 2x/day on day 1, then 600 mg 2x/day on days 2-5. The other treatment such anticoagulant, vitamin C and D and nutrition of all patients were the same in the wards.

The exclusion criteria of this study were as follows: being non COVID-19 patient, children who under 18 years, and pregnancy. All patients were not yet vaccinated against the corona virus.

Decreased oxygen saturation and PaO_2/FiO_2 rate, increased respiration rate with worsening clinical condition and elevated inflammatory parameters such CRP, ferritin, D-dimer, creatinine, lactate and troponin were accepted as criteria for admission to ICU. Demographic and clinical characteristics, and the ICU admission rate, the discharge from the ward and mortalities were compared between the two groups.

Statistical analysis

A statistical package program was used for statistical analysis of the data obtained in this study. Kolmogorov-Smirnow test was used to check for the normality of data distribution. Continuous variable with normal distribution were presented as mean ± standard deviation (SD). To compare the categorical data, Pearson's Chi-square test and Fisher's exact test were used. The t-test was used for the comparisons of the two groups. A $p<0.05$ was accepted as statistically significant.

Results

A total of 2734 patients were analyzed retrospectively and divided into H (n=1123 patients) and F (n=1611patients) groups. The main reasons for hospitalization were fatigue, shortness of breath, fever, low oxygen saturation and positive PCR test with computerized chest tomography findings for COVID-19 in all patients. Age, gender, Body Mass Index (BMI), Charlson Comorbidity Index (CCI), mean blood pressure, heart rate, respiratory rate and oxygen saturation were not significant different between the H and F groups at admission (Table 1).

Table 1 Comparison of demographic and clinic characteristic of the H and F Groups

	H Group (n=1123)	F Group (n=1611)	*P* value
Age (years)	68.3±13	69.1±12	0,0977
Gender (M/F)	584/539	823/788	0,6648
BMI (kg/m^2)	33,2±6	33,5±8	0,2869
Charlson Comorbididty Index	6,2±2	6,3±3	0,3291
Mean blood pressure (mmHg)	85,2±24	83,6±26	0,1025
Heart rate (beats/ minute)	102,2±24	104,2±22	0,0717
Respiration rate (per minute)	33,8±7	34,3±8	0,0909
Oxygen saturation (%)	85,6±10	86,2±9	0,1016

*$p<0.05$ is statistically significant

The treatments of the patients in the wards such the support of oxygen with reservoir mask, enoxaparin as an anticoagulant, acetylcysteine to loss mucus in the airways, steroid use, vitamin C and D, and patient's nutrition were the same. The ICU admission criteria (decreased oxygen saturation or PaO_2/FiO_2 rate, increased respiration rate with worsening clinical condition and elevated inflammatory parameters such CRP, ferritin, D-dimer and creatinine, lactate, troponin) were similar between the two groups.

The rate of discharged from the ward was significantly ($p<0.001$) higher in the H group when compared with F group as 85,75% versus 73,74%. Duration of the wards was longer in the H group when compared than the F group ($p<0.01$). In addition, the ICU admission rate was significantly ($p<0.001$) lower in the H group than F group as 9,79% versus 20,54% (Table 2).

Table 2 Comparison of the ICI admission rate, discharged from the ward and mortalities of the H and F Groups

	H Group (n=1123)	F Group (n=1611)	*P* value
Duration of the ward (days)	6,7±3,4	6,3±3,2	0,0017*
Discharge from the ward	93/1123=85,75%	1188/1611=73,74%	0,0001*
The ward mortality rate	50/1123=4.45%	92/1611=5,71%	0,1697
the ICU admission rate	110/1123=9,79%	331/1611=20,54%	0,0001*
ICU mortality	51/110=46,36%	119/331=35,95%	0,0672
Total mortality	101/1123=8,99%	211/1611=13,09	0,0011*

*$p<0.05$ is statistically significant

The ward mortality and ICU mortality rates were not significant different between the two groups. However, total mortality rate, considering of the total ward and ICU, was significantly lower in The H group ($p<0.01$), (Table 2).

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Minimal side effects were recorded in the follow-up of the patients in the wards. QT interval prolongation was observed in 43 (43/1123=0,038%) patients in the Hydroxychloroquine group. Liver enzyme elevations such as AST and ALT were recorded in 76 (76/1611=0,047%) patients in the Favipiravir group.

Discussion

Many drugs were used, such as hydroxychloroquine and favipiravir, which were thought to have a potential effect against COVID-19 since there was no cure yet. In this study, we investigated the effects of hydroxychloroquine and favipiravir administered in hospitalized patients with COVID-19 on discharge from the service, length of stay in the ward, admission to intensive care unit and mortality.

Chloroquine and its metabolite hydroxychloroquine were used to treat malaria and some auto-immune diseases such rheumatoid arthritis (RA), systemic lupus erythematous (SLE), and juvenile idiopathic arthritis due to its immunosuppressive effects. In an experimental study, Yao X and colleagues[10] reported that the antimalarial drugs hydroxychloroquine and chloroquine had in vitro antiviral effects, immune modulating effects and can suppress the increased of immune factors. In addition, in another study, it was reported that the hydroxychloroquine and chloroquine could decrease the various activations of corona virus such as duration of symptoms and worsening of pneumonia, and reinforced this with radiological correction.[11] However, some studies[12,13] have reported that hydroxychloroquine has no positive effect on hospital mortality in COVID-19 patients. Rosenberg and colleagues[12] reported that treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment of the patients with COVID-19, was not significant associated with differences in hospital mortality in a retrospective multicenter cohort study. But some data about the patient characteristics of this study were examined in detail, one can understand that there are some methodological problems in this study. For example, the data of Hydroxychloroquine plus Azithromycin Group were worse than the data of Neither Drug Group ($p<0.01$). These data were obesity, any chronic lung conditions, rapid respiratory rate, oxygen saturation, elevated AST and ALT values and abnormal chest imaging findings. Of course, it is known that these data are associated with higher mortality. One can understand that the cause of higher mortality in the Hydroxychloroquine plus Azithromycin Group was associated with higher comorbid conditions in this group.

Favipiravir is an RNA dependent RNA polymerase inhibitor, and it was used to treatment of COVID-19 in some studies in China. Dong and colleagues reported that Favipiravir shows more potent antiviral activity than lopinavir/ritonavir in the treatment of patients with COVID-19 without significant side effects.[14] In addition, in an observation study resulted that although it has been done in a limited number of patients, Favipiravir may be more useful than lopinavir/ritonavir in terms of effective use in Intensive Care Unit.[15]

There are very few studies comparing the efficacy and side effects of hydroxychloroquine and favipiravir on COVID-19 patients. In this study, we compared the use of hydroxychloroquine and favipiravir in the wards and then in the ICUs in a large patient groups with COVID-19 (1123 patients in group H and 1611 patients in group F). The admission rate from the ward to the ICU, the discharge from the ward and mortality were the endpoints of this study. The admission rate from the ward to the ICU was significantly lower in group Hydroxychloroquine than in group Favipiravir. In parallel with this, the rate of discharge from the ward was higher in group Hydroxychloroquine. Hydroxychloroquine and Hydroxychloroquine plus Favipiravir were compared in mild and moderate covid-19 patients in a single-center retrospective observational study. It was stated in the results of this study that the Hydroxychloroquine and Hydroxychloroquine plus Favipiravir groups decreased the percentage of intensive care admissions compared to the Favipiravir group alone.[16] However, it has been reported in another study that taking Hydroxychloroquine and Favipiravir together does not provide clinical benefits in moderate and severe COVID-19 patients.[17] Our study results demonstrated that the use of hydroxychloroquine in the ward decreased the admission rate to the ICU when compared favipiravir use in COVID-19 patients. Considering this result, it is not surprising that the rate of discharge from the ward was higher in the Group H compared to the Group F.

As for the side effects, it has been reported that the incidence of prolonged QT interval increases with the use of hydroxychloroquine.[12,13] Favipiravir is associated with higher ALT and AST levels when compared hydroxychloroquine in COVID-19 patients.[18] In our study, the side effects observed in the Hydroxychloroquine and Favipiravir groups were minimal. QT interval prolongation was observed in 43 (0,038%) patients in the H group, and liver enzyme elevations such as AST and ALT were observed in 76 (0,047%) patients in the H group in the wards.

Conclusion

This retrospective study showed that hydroxychloroquine lowers the ICU admission rate and raises the discharge rate when compared with favipiravir in the ward patients with COVID-19. However, it does not change the ward and the ICU mortality rates.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publications of this paper.

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