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Original Scientific Paper

EFFECTS OF HYDROXYCHLOROQUINE PLUS FAVIPIRAVIR TREATMENT ON THE CLINICAL COURSE AND BIOMARKERS IN HOSPITALIZED COVID-19 PATIENTS WITH PNEUMONIA

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SUMMARY – Background: The novel coronavirus disease 2019 (COVID-19) has a broad spectrum of clinical manifestations, the most common serious clinical manifestation of the coronavirus infection being pneumonia. Unfortunately, the optimal treatment approach is still uncertain. However, many studies have been conducted on the effectiveness of several medications in the treatment of COVID-19 infection. The aim of this study was to evaluate the effectiveness of the hydroxychloroquine (HCQ) + favipiravir (FAV) treatment regimen and HCQ alone by comparing the patient's clinical response and laboratory results on the fifth day of treatment in patients hospitalized due to COVID-19 infection.

Patients and methods: This retrospective cohort study was conducted in Malatya Training and Research Hospital between March 2020 and July 2020. The study included 69 patients with confirmed COVID-19 with pneumonia. The patients were divided into 2 groups, those receiving HCQ alone and those receiving the HCQ + FAV combination.

Results: A total of 69 patients were included in the study, and the mean age was 60.09±15.56 years. A statistically significant decrease was observed in C-reactive protein (CRP) levels, at the end of the fifth day, in patients who received HCQ + FAV treatment (p=0.002), whereas there was no decrease in CRP levels in patients who received HCQ treatment alone. In addition, an increase in lymphocyte count and a better fever response was observed at the end of the fifth day in patients who received HCQ + FAV (p=0.008). However, there was no statistical difference between both treatment regimens in terms of hospital stay and treatment results (p=0.008, p=0.744, p=0.517).

Conclusion: Although the combination of HCQ + FAV treatment was observed to be effective on CRP levels and fever response in patients with COVID-19 pneumonia, there was no difference in terms of hospital stay and discharge.

Key words: *Favipiravir; hydroxychloroquine; COVID-19; SARS-COV-2; pneumonia*

Introduction

In December 2019, the novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in Wuhan, China. It has continued to spread rapidly over

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many countries and has led to a global pandemic[1-3]. Unfortunately, effective vaccines have not yet been developed, and the optimal treatment approach is uncertain. On the other hand, social distancing, quarantine and isolation are the best way to reduce the spread of COVID-19[4-6].

COVID-19 has a broad spectrum of clinical manifestations. Even though it usually causes common cold symptoms, up to 20% of patients develop pneumonia and severe illness that requires supplemental oxygen therapy. Moreover, approximately 5% of patients develop critical illness with respiratory failure, multi-organ dysfunction and death[6-9].

Although an effective treatment regimen has not been defined, many studies have been conducted in order to investigate the effectiveness and reliability of several drugs, including chloroquine/hydroxychloroquine, remdesivir, lopinavir / ritonavir and favipiravir in the treatment of COVID-19[10]. The list of antiviral drugs believed to be effective in the treatment of COVID 19 is included in the guidelines that have been prepared and updated by the Scientific Advisory Board of Ministry of Health of the Republic of Turkey[11].

The aim of this study was to compare the effectiveness of a hydroxychloroquine (HCQ) + favipiravir (FAV) combination and a treatment regimen of HCQ alone in the treatment of COVID-19, by evaluating the laboratory data and treatment results at the end of the fifth day in patients who were hospitalized for COVID-19 pneumonia.

Patients and methods

Study design and data collection

This single-center retrospective cohort study was conducted in the COVID-19 wards of the Malatya Training and Research Hospital between March 20, 2020 and July 31, 2020. A total of 69 confirmed COVID-19 patients with pneumonia were enrolled in the study. The patients who received only HQ as a treatment for COVID-19 pneumonia and those who received HCQ + FAV were included in the study. Patients transferred to the critical care unit at the time of admission were excluded from the study. Inclusion and exclusion criteria are summarized in Table 1.

A confirmed case was defined as a patient with positive SARS-CoV-2 real-time reverse transcription polymerase chain reaction (RT-PCR) from nasopharyngeal and/or oropharyngeal swab. A COVID-19 pneumonia case was defined as a symptomatic COVID-19 case that had pulmonary ground glass opacities and/or infiltrates visible in computed tomography of the thorax[11,12]. Decisions on the treatment and discharge of the patients were performed according to the guidelines published by Scientific Advisory Board of the Republic of Turkey Ministry of Health[11].

The following data were recorded and analyzed: demographic features of patients (age, gender), comorbidities, patients symptoms (fever, cough, dyspnea, myalgia, fatigue, smell or taste loss, diarrhea) and vital signs (body temperature, heart rate, respiratory rate, blood pressure, oxygen saturation), pneumonia severity index (PSI) and CURB-65 score, the first-day and fifth-day laboratory findings of the patients (complete blood count, C-reactive protein (CRP), procalcitonin (PCT), ferritin, albumin, lactate dehydrogenase (LDH), D-dimer), length of hospital stay and treatment outcomes (discharge, transfer to the intensive care unit or exit from the COVID-19 wards).

The patients were divided into two groups: those who received HCQ alone and those who received HCQ + FAV together. The data of the patients in both groups at the time of hospitalization and on the fifth day, the effect of treatment regimens on laboratory data,

Table 1. Inclusion and exclusion criteria in the present study

Inclusion criteria in the study	Exclusion criteria in the study
≥ 18 years old	< 18 years old
Confirmed COVID-19 case	Possible COVID-19 case
COVID-19 patients with pneumonia	COVID-19 patients without pneumonia
COVID-19 patients treated with Hydroxychloroquine ∓ favipravir	Patients transferred to the critical care unit at the time of admission
COVID-19 patients hospitalized in the COVID-19 ward	Outpatients

the presence of fever at the end of the fifth day, length of stay and treatment results were evaluated and compared.

Statistical analysis

The data obtained from the hospital database were adjusted and transferred into Microsoft Excel tables. Normally distributed data were given as mean value ± standard deviation; data which were not normally distributed were given as median (min-max) values, numbers and percentages. The distribution of variables was controlled using the Skewness & Kurtosis test. The independent samples t test was used for the analysis of the parametric data in comparisons between two independent groups; the Mann Whitney U test was used for the non-parametric data, and the Chi-square test was used for the categorical data. The dependent samples t test was used in comparisons of parametric data from two groups with dependent variables, while the Wilcoxon test was used in comparisons of non-parametric data, and the McNemar test was used in comparisons of categorical data. All statistical analyses were performed using SPSS (Statistical Package for Social Sciences) for Windows 23.0 software. Results were evaluated at a 95% confidence interval, and a value of $p < 0.05$ was accepted as statistically significant.

Ethics

The study protocol was approved by the Turkish Ministry of Health and Clinical Ethics Committee of Inonu University (protocol code:2020/124). A written informed consent form was not obtained due to the retrospective nature of the study.

Results

Of the 69 cases included in the study, 34 (49.3%) were men, 35 (50.7%) were women, and the mean age was 60.09±15.56 years. At the time of admission, 45 (65.2%) of the cases were found to have a comorbid disease. The most common comorbid diseases were hypertension (50.7%), diabetes mellitus (29%), chronic ischemic heart disease (23.2%) and chronic obstructive pulmonary disease (14.5%). The most common complaints of the patients at admission were cough in 48 (69.6%) patients and shortness of breath and fever in 44 (63.8%) patients (Table 2).

Table 2. Baseline characteristics of the patients

	All patients (n=69)
Mean age, years (Me±SD)	60.09±15.56
Gender	
Female	35 (50.7%)
Male	34 (49.3%)
Comorbidities	
Hypertension	35 (50.7%)
Diabetes mellitus	20 (29.0%)
Chronic ischemic heart disease	16 (23.2%)
Chronic obstructive pulmonary disease	10 (14.5)
Alzheimer disease	7 (10.1%)
Congestive heart failure	5 (7.2%)
Cerebrovascular disease	2 (2.9%)
Malignancy	1 (1.4%)
Onset symptoms	
Cough	48 (69.6%)
Dyspnea	44 (63.8%)
Fever	44 (63.8%)
Fatigue	42 (60.9%)
Myalgia	8 (11.6%)
Diarrhea	8 (11.6%)
PSI	85.32±24.75
CURB-65	1.84±0.90

Me: mean; **SD:** standard derivation; **PSI:** pneumonia severity index

The cases were divided into two groups: patients who received HCQ alone (n=35) and those who received the HCQ + FAV combination (n=34) as the COVID-19 treatment regimen. There were no statistically significant differences between the two groups in terms of pneumonia severity index, CURB-65 score and peripheral capillary oxygen saturation (SpO_2) values in room air (p=0.434, p=0.676) (Table 3).

Table 3. Comparison of pneumonia severity at admission to the hospital

	Hydroxychloroquine group (n=35)	Hydroxychloroquine + Favipiravir group (n=34)	P value
PSI	83.00±23.00	87.71±26.57	0.434*
CURB-65	1.89±0.96	1.79±0.84	0.676*
SpO_2	91.65±2.87	92.74±3.01	0.127*

Me: mean; **SD:** standard derivation; **PSI:** pneumonia severity index
*Independent samples t test

Table 4. Effects of treatment regimens on laboratory findings and fever on day five

	Hydroxychloroquine group (n=35)			Hydroxychloroquine + Favipiravir group (n=34)		
	Day 0	Day 5	P value	Day 0	Day 5	P value
CRP, mg/dL (min-max)	4.47 (0.21-24.17)	2.36 (0.16-16.38)	0.502*	7.59 (0.41-35.62)	3.46 (0.30-19.95)	**0.002***
PCT, ng/mL (min-max)	0.07 (0.02-0.85)	0.06 (0.02-0.39)	**0.047***	0.10 (0.04-4.25)	0.07 (0.03-1.65)	**0.023***
Wbc, cells/mL (min-max)	5530 (2400-9990)	6000 (2760-9910)	0.806*	6975 (2750-3817)	6975 (2750-3817)	0.945*
Neu, cells/mL (min-max)	3680 (1480-8270)	4310 (1370-8050)	0.928*	4835 (1520-3422)	4615 (1510-1277)	0.478*
Lymph, cells/mL (min-max)	1570 (500-4390)	1460 (540-3880)	0.863*	1245 (470-2430)	1395 (690-3020)	0.393*
NLR, (min-max)	2.24 (0.98-11.33)	2.52 (0.89-9.41)	0.974*	3.21 (1.50-16.37)	3.29 (0.90-9.20)	0.437*
LDH, IU/L (Me±SD)	294.23 ±79.21	334.74 ±166.27	0.846**	363.53 ±122.98	363.94 ±114.28	0.218**
Ferritin, ng/mL (Me±SD)	278.09 ±253.93	362.12 ±386.49	**<0.001****	470.57 ±362.31	604.78 ±489.97	**<0.001****
Albumin, g/dL (Me±SD)	3.77 ±0.39	3.56 ±0.51	**<0.001****	3.50 ±0.41	3.28 ±0.43	**0.001****
D-dimer, mcg/mL (min-max)	0.336 (0.01-4.64)	0.338 (0.05-4.30)	0.896*	0.45 (0.04-16.40)	0.58 (0.08-7.13)	0.146*
Fever	21/35 (60%)	8/35 (22.9%)	**<0.001*****	21/34 (61.8%)	1/34 (2.9%)	**<0.001*****

CRP: C-reactive protein**; PCT:** procalcitonin**; CBC:** complete blood count**; Wbc:** white blood cell**; Neu:** neutrophil**; Lymph:** lymphocyte**; LDH**: lactate dehydrogenase**; NLR:** neutrophil lymphocyte ratio**; Me:** mean; **SD:** standard derivation
*Wilcoxon Test
** Paired T Test
*** McNemar Test

When the effects of both treatment regimens on complete blood count and acute phase reactants were evaluated at the end of the fifth day, a significant decrease in CRP was observed in patients who received HCQ+FAV treatment, whereas there was no decrease in patients who received only HQ treatment (p=0.002, p=0.502, respectively). In addition, an increase in lymphocyte count was observed in patients who received HCQ+FAV treatment; however, it was not statistically significant (p=0.393). on the other hand, a decrease in lymphocyte count was observed at the end of the fifth day in patients who received only HQ treatment (Figure 1) (Table 4).

Although a better fever response was observed at the end of the fifth day in patients who received HCQ + FAV combination therapy, there were no statistical differences in hospitalization times and treatment results between the patients in both treatment regimens (p=0.008, p=0.744, p=0.517) (Table 5).

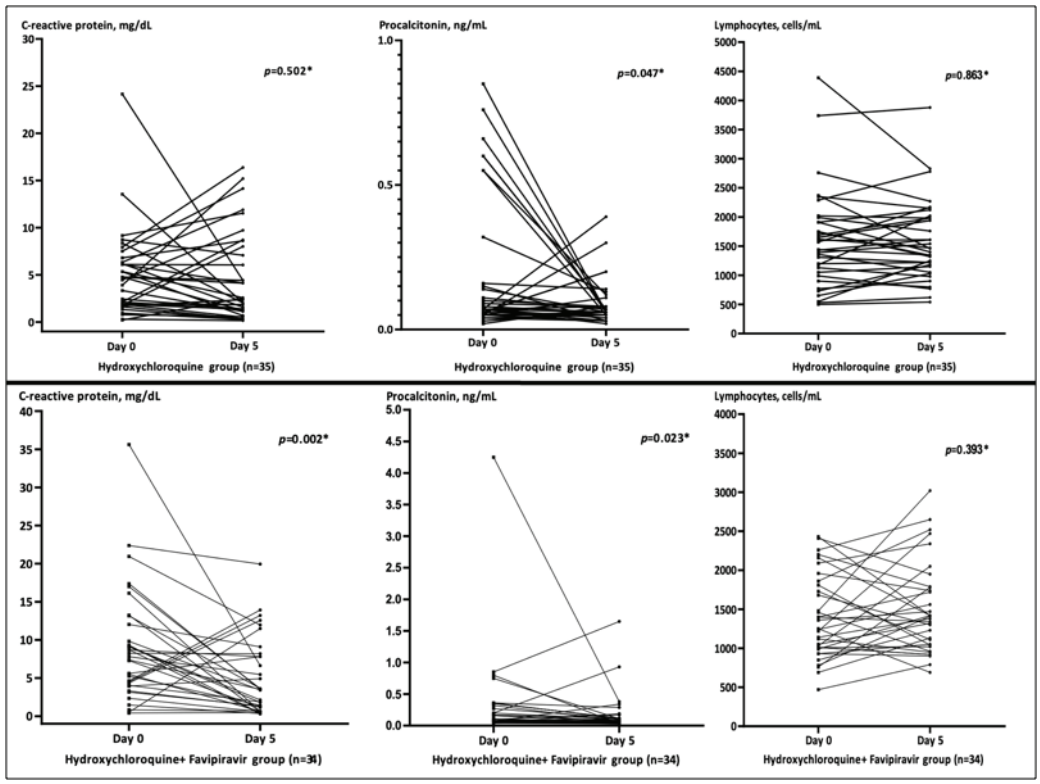

Fig. 1. Changes in laboratory findings before and after treatment in patients with COVID-19 pneumonia

Table 5. Comparison of the treatment outcomes

	Hydroxychloroquine group (n=35)	Hydroxychloroquine + Favipiravir group (n=34)	P value
Hospital LOS, days (Me+SD)	8.60±2.63	8.79±2.26	0.744*
Fever recovery	13/21 (62%)	20/21 (95%)	0.008**
Outcome **Discharge** **Transfer to the ICU**	 31 (88.5%) 4 (11.5%)	 31 (91.1%) 3 (8.9%)	0.517**
Me: mean; **SD:** standard derivation; **LOS:** length of stay; **ICU:** intensive care unit *Independent samples t test **Chi-squared test			

Discussion

In our study, we observed a statistically significant decrease in CRP at the end of the fifth day in patients who received HCQ+FAV treatment (p=0.002); there was no CRP decrease in patients who received only HCQ treatment. In addition, an increase in lymphocyte count was observed at the end of the fifth day in patients who received HCQ+FAV; however, the difference was not statistically significant. On the other hand, a decrease in lymphocyte count was observed at the end of the fifth day in patients who received only HCQ treatment. Better fever recovery was observed at the end of the fifth day in patients who received HCQ + FAV compared with patients who received HCQ treatment alone (p=0.008). However, there was no statistical difference between the two treatment regimens in terms of hospital stay and treatment results (p=0.744, p=0.517).

Coronaviruses are single-stranded, positive-polar enveloped RNA viruses with petal-shaped projections on their surfaces[13]. The clinical presentation of the coronavirus disease is highly variable. The spectrum of the disease can vary greatly, ranging from the common cold to severe acute respiratory failure[13-15].

However, the risk of severe disease, associated with a decreased immune response, increases in elderly patients and patients with comorbidities[16-19]. Cao et al., in a meta-analysis in which they evaluated the clinical features and imaging findings of COVID-19 cases, reported that 35.6% of COVID-19 cases have at least one comorbid disease[20]. Hypertension, cardiovascular diseases, diabetes mellitus and chronic obstructive pulmonary disease are the most common comorbid diseases in COVID-19 cases[19,20]. In our study, the mean age of the patients was 60.09 ± 15.56 years, and 65.2% of them had at least one comorbid disease; we attribute the high rate of patients with comorbidities compared with the literature to the inclusion of only pneumonia cases in our study.

The average incubation period of the disease in COVID-19 cases is 3-7 days. The most common symptoms at the time of admission include fever, cough, fatigue, and shortness of breath. Other symptoms including sputum, headache, hemoptysis and diarrhea have also been reported[17,21-25]. Consistent with the literature, the most frequently observed symptoms at the time of admission in our study were cough (69.6%), shortness of breath (63.8%), fever (63.8%) and fatigue (60.9%).

Pneumonia, which is the most serious and most common picture of the disease, can develop in 20% of COVID-19 cases and manifests in lung imaging as bilateral ground glass infiltrations. Hypoxia develops in this period, which is called the pulmonary phase of the disease, and hospitalization is required for almost all patients[7,8,26].

Agents used in the treatment of COVID-19 have been selected by considering the clinical experiences and data obtained in the SARS-CoV, MERS-CoV and Ebola outbreaks in previous years. However, the most appropriate approach in the treatment of COVID-19 is still unclear. Treatment approaches can be classified under three main headings: potential anti-viral agents, organ-specific supportive therapies and immunomodulators[8,27,28].

A number of scientific studies evaluating the efficacy and safety of potential anti-viral agents including chloroquine/hydroxychloroquine, lopinavir/ritonavir, remdesivir and FAV have been conducted. Although the efficacy of medications used for the treatment has been demonstrated in a limited number of studies, many medications have been widely used in COVID-19 patients all over the world, either alone or in combination, due to the urgency of the pandemic[27,28]. Similarly, the use of HCQ and FAV, which have anti-viral properties, is recommended by the Republic of Turkey Ministry of Health Scientific Advisory Board in the updated guideline for the treatment of COVID-19 pneumonia[11]. In addition, in our country it is recommended to initiate potential anti-viral therapy in the early disease period, since delaying the treatment until the clinical picture of the cases becomes severe may miss the early treatment opportunity, when the course of the disease can be changed more easily[11,28].

Chloroquine/hydroxychloroquine is an inexpensive and reliable drug that has been used in the treatment and prophylaxis of malaria for many years and has been used for many autoimmune diseases, especially rheumatoid arthritis, due to its anti-inflammatory properties. In in vitro studies, it has been found that chloroquine/hydroxychloroquine reduces viral replication and viral spread and also acts as an immunomodulator by inhibiting the release of inflammatory cytokines such as IL-6 and TNF-α[28-32].

Although the effectiveness of chloroquine/hydroxychloroquine in the treatment of COVID-19 has been demonstrated in in vitro studies, there is

a limited number of clinical studies, and the results obtained from these studies are contradictory. In early studies, was shown that chloroquine treatment leads to improvement in infiltrations observed in lung tomography, improvement in disease progression, and better fever response[33,34]. Similarly, in a randomized clinical study conducted by Chen et al., it was shown that HCQ treatment provided better improvement in pneumonia symptoms and fever response in a shorter period in COVID-19 cases with pneumonia[35]. However, in another prospective randomized controlled study conducted in China, it was shown that HCQ does not reduce nasopharyngeal viral clearance at the end of the seventh day compared with conventional treatment in COVID-19 cases, and there was no difference between the progression rates in radiological findings between both treatments[36]. In addition, in the study by Mahévas et al., it was shown that, in COVID-19 pneumonia cases who were followed up in the ward and needed oxygen, HCQ treatment had no effect on survival and reduction of transfer to the intensive care unit, compared with conventional treatment. In addition, in that study it was reported that 20.2% of the cases in the group receiving HCQ treatment and 24.7% of the cases in the control group had been transferred to the intensive care unit[37]. In our study, although a significant fever response was observed at the end of the fifth day of treatment in patients receiving HCQ alone, no statistically significant decrease was observed in the CRP values. However, a decrease in lymphocyte count was observed at the end of the fifth day in the patients who received HCQ treatment alone. In our study, 4 (11.5%) of the patients who received HCQ treatment alone were transferred to the intensive care unit. This rate was found to be lower compared with the literature.

Favipiravir is an agent that inhibits viral replication by inhibiting ribonucleic acid (RNA) dependent RNA polymerase. In studies, it has been shown that it is effective in the treatment for Ebola and influenza, which are RNA viruses. Similarly, although it has been shown in an in vitro study that FAV was effective against the RNA virus SARS-CoV-2, there are few clinical studies supporting the use of FAV in the treatment of COVID-19[28,30,31,38]. In a limited number of studies evaluating the effectiveness of FAV in the treatment of COVID-19, it has been shown that FAV treatment significantly increases viral clearance and radiological recovery and also provides better improvement in cough and fever[39,40]. In our study, a significant fever response was observed in patients who received FAV + HCQ combination therapy at the end of the fifth day and an increase in lymphocyte count was observed in the patients, although it was not statistically significant ($p<0.001$, $p=0.393$). In addition, a better fever response was observed at the end of the fifth day of the treatment in patients who received FAV + HCQ combination therapy compared with the patients who received HCQ treatment alone ($p=0.008$).

Various clinical studies and meta-analyses have focused on the identification of the risk factors for progression and mortality in patients with COVID-19[41,42]. Laboratory findings including increased levels of CRP, ferritin, LDH, D-dimer and decreased blood lymphocyte counts have been found to be associated with clinical worsening and mortality in hospitalized patients with COVID-19[42-45]. Sharifpour et al. found that CRP levels in patients with COVID-19 increased linearly during the first week of hospitalization and peaked on day five[46]. Additionally, increased levels of CRP in patients with COVID-19 could be an early marker for the prediction of disease severity[47].

Consistent with previous clinical studies, patients transferred to the intensive care unit in both groups had increased serum levels of CRP, LDH, ferritin and D-dimer in the present study. Moreover, patients transferred to the ICU had lower serum albumin levels and lymphocyte counts. However, no statistical difference was found in terms of hospital stay and discharge rates in patients receiving FAV + HCQ combination therapy.

Limitations

The present study had some limitations. It was a single-center retrospective cohort study and the sample size in the study was relatively small.

Conclusion

Although HCQ + FAV treatment had a better effect on CRP and fever response in hospitalized cases of COVID-19 pneumonia compared with HCQ treatment alone, no significant differences in hospital stay, transfer to the intensive care unit and discharge were found. Further prospective randomized controlled studies with larger patient numbers are needed.

Conflict of interest:

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Sažetak

UČINCI LIJEČENJA HIDROKSIKLOROKINOM PLUS FAVIPIRAVIROM NA KLINIČKI TOK I BIOMARKERI U HOSPITALIZIRANIH PACIJENATA S COVID-19 I UPALOM PLUĆA

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Pozadina: Bolest uzrokovana novim koronavirusom 2019 (COVID-19) ima širok spektar kliničkih manifestacija, pri čemu je upala pluća najčešća ozbiljna klinička manifestacija infekcije koronavirusom. Nažalost, optimalni pristup liječenju još uvijek nije jasno utvrđen. Ipak, provedeno je mnogo studija koje su istraživale učinkovitost raznih lijekova u liječenju infekcije COVID-19 virusom. Cilj ove studije bio je utvrditi učinkovitost liječenja kombinacijom hidroksiklorokina (HCQ) i favipiravira (FAV) te liječenja isključivo HCQ-om, uspoređivanjem kliničkog odgovora pacijenata na liječenje i njihovih laboratorijskih rezultata nakon pet dana liječenja u pacijenata hospitaliziranih zbog infekcije virusom COVID-19.

Pacijenti i metode: Ova retrospektivna kohortna studija provedena je u Malatya Training and Research Hospital između ožujka 2020. i srpnja 2020. Uključivala je 69 pacijenata s potvrđenom infekcijom virusa COVID-19 sa upalom pluća. Pacijenti su podijeljeni u dvije skupine, od kojih je jedna primala samo HCQ, a druga kombinaciju HCQ + FAV.

Rezultati: U studiju je uključeno ukupno 69 pacijenata s prosječnom dobi od 60,09±15,56 godina. Zamijećena je statistički značajno smanjenje u razini C-reaktivnog proteina (CRP) na kraju petog dana liječenja u pacijenata koji su primali HCQ + FAV (p=0,002), a nije bilo smanjenja u razini CRP-a u pacijenata koji su primali samo HCQ. Uz to, u pacijenata koji su primali HCQ + FAV zamijećeno je i povećanje u broju limfocita te bolji odgovor na vrućicu na kraju petog dana liječenja (p=0,008). Ipak, nije bilo statističke razlike između ta dva režima liječenja u odnosu na trajanje hospitalizacije i rezultata liječenja (p=0,008, p=0,744, p=0,517).

Zaključak: Iako je kombinacija HCQ + FAV bila učinkovita glede razine CRP-a i odgovora na vrućicu u pacijenata sa upalom pluća uzrokovanom COVID-19 virusom, nije bilo razlike u trajanju hospitalizacije i otpusta iz bolnice.

Ključne riječi: *favipiravir; hidroksiklorokin; COVID-19; SARS-COV-2; upala pluća*