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Covid-19'un Yoğun Bakım Yönetiminde Uzatılmış Hidroksiklorokinin Sağkalım ve Maliyetler Üzerindeki Etkisi

The Effect of Extended Hydroxychloroquine in Intensive Care Management of Covid-19 on Survival and Costs

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ÖZ

GİRİŞ ve AMAÇ: *Hidroksiklorokin, çoğu koronavirüse ve özellikle SARS-CoV-2 dahil olmak üzere virüslere karşı geniş bir etki yelpazesi vardır. Ulusal tedavi kılavuzlarındaki hidroksiklorokin tedavi önerisi pandeminin başlangıcında 5 gün iken, 14 Nisan'dan itibaren hidroksiklorokin tedavisi altında kliniğin kötüleştiği durumlarda 10 gün olarak önerilmiştir. Bu retrospektif, gözlemsel, tek merkezli çalışmada, yoğun bakımda COVID-19 ile izlenen hastalarda hidroksiklorokin tedavi süresinin hastanede kalış günü, mekanik ventilasyon gereksinimi, süresi, sağkalıma ve maliyet üzerine etkisinin ortaya çıkarılması amaçlanmıştır.*

YÖNTEM ve GEREÇLER: *Etik Kurul onayının ardından 5 gün süreyle hidroksiklorokin alan ilk 50 hastanın (Grup 1) ve 10 gün alan ilk 50 hastanın (Grup 2) verileri çalışmaya dahil edildi. Hastaların yaşı, cinsiyeti, ek hastalıkları, COVID-19 testleri, hidroksiklorokin tedavi günleri, invazif mekanik ventilatör ihtiyacı ve süresi, yoğun bakımda yatış günü, mortalite varlığı ve maliyetleri kaydedildi.*

BULGULAR: *Grup 2'deki hastaların hastanede kalış süresi grup 1'den daha uzundu (9,4 güne karşı 13,8 gün, p = 0 <0001). Mortalite açısından gruplar arasında fark yoktu (sırasıyla % 68, % 62, p = 0.383). Grup 2'de yoğun bakımda yatış maliyeti daha yüksekti.*

TARTIŞMA ve SONUÇ: *Bu retrospektif gözlemsel çalışmada 10 günlük tedavi alımının mekanik ventilatör ihtiyacını ve mortaliteyi etkilemediği, yoğun bakımda yatış süresini uzattığı ve maliyetini önemli ölçüde artırdığı ortaya konulmuştur.*

Anahtar Kelimeler: *Koronavirüs, maliyetler, hidroksiklorokin, yoğun bakım üniteleri, ölüm oranı.*

ABSTRACT

INTRODUCTION: *There is a broad spectrum of action against most coronaviruses and especially viruses, including SARS-CoV-2. While the hydroxychloroquine treatment recommendation in the national treatment guidelines was 5 days at the beginning of the pandemic, it was recommended as 10 days in cases where the clinic deteriorated under hydroxychloroquine treatment since 14 April. In this retrospective, observational, single-center study, it was aimed to reveal the effect of hydroxychloroquine treatment duration on the day of hospitalization, mechanical ventilation requirement, duration, survival and cost in patients with COVID-19 in intensive care unit.*

METHODS: *Following the approval of the Ethics Committee, the data of the first 50 patients (Group 1) who received hydroxychloroquine for 5 days and the first 50 patients (Group 2) who received 10 days were included in the study. Patients' age, gender, additional diseases, COVID-19 testings, hydroxychloroquine treatment days, invasive mechanical ventilator requirement and duration, intensive care hospitalization day, mortality and costs were recorded.*

RESULTS: *The duration of hospitalization in patients in group 2 was longer than group 1 (9,4 days vs 13,8 days, p=0<0001). There was no difference between the groups in terms of mortality (68%, 62%, respectively, p=0.383). The cost of intensive care unit hospitalization was higher in Group 2.*

DISCUSSION AND CONCLUSION: *In this retrospective observational study, it was found that 10 days of treatment intake did not affect the need for mechanical ventilator and mortality, while extending the intensive care hospitalization period and significantly increasing its cost.*

Keywords: *Coronovirus, costs, hydroxychloroquine, intensive care units, mortality*

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INTRODUCTION

Severe Acute Respiratory Syndrome, which appeared in Wuhan Province of China and was named as COVID-19 by the World Health Organization (WHO) as of December 2019, has caused a pneumonia associated with SARS-CoV-2 (1,2). The disease spread rapidly over the world in 3 months and was declared as an epidemic by WHO on March 11, 2020. Various treatment methods have been tried and vaccine development studies have started for the virus, which has influenced the whole world.

Chloroquine has a wide spectrum of action against many coronaviruses including SARS-CoV-2, and coronavirus cell entry occurs along the endo-lysosomal pathway (3). Studies were initiated to investigate the possible effect of chloroquine against SARS-CoV-2 since it is an emergency that threatens public health. Studies have shown that both chloroquine and antiviral drug remdesivir inhibit SARS-CoV-2 in vitro, and these drugs have been suggested to be used in COVID-19 patients (4).

Inhibition of virus binding to host cells (5), inhibition of viral release into the intracellular space by disruption of the lysosome-endosome fusion (6,7) and inhibition of the release of pro-inflammatory cytokines (7) are some possible mechanisms of action of hydroxychloroquine (HCQ) against SARS-CoV-2. Described in vitro antiviral properties of chloroquine (CQ) have been confirmed during treatment of some patients infected with the virus; however, the same success did not always repeat in clinical trials.

A non-randomized study from France showed that HCQ plus azithromycin (AZ) therapy reduce the viral load in COVID-19 patients (8). After this study, another group from France reported that co-administration of HCQ and azithromycin did not have a strong antiviral activity in severely affected COVID-19 patients (9). Clinical studies from China show that HCQ reduces the risk of the progression of the disease to the severe stage in COVID-19 patients (10,11).

CQ and HCQ overdose is highly toxic and leads to central nervous system toxicity presenting seizures and coma. It may also cause rapid onset of cardiovascular failure (12). The most commonly known and feared side effect in combined therapy with AZ is QT prolongation. For this reason, close cardiac monitoring and electrocardiography (ECG) is recommended. It has been stated among the adverse effects that HCQ causes toxicity in retinal tissue and it may result in irreversible retinopathy, especially when patients are exposed to the drug for a long time (13,14). In less recurrent cases, usually after prolonged exposure to HCQ, cardiotoxicity, and toxicological effects were reported in the central nervous system with neuromyopathy symptoms such as skeletal muscle weakness and gastrointestinal changes (15). Despite all these effects, the potential use of these drugs for COVID-19 is supported by factors such as low cost and history of use in the treatment of rheumatic and infectious diseases including malaria, whereas the research on the use of CQ and HCQ in the management of COVID-19 has just started. Emergency use of HCQ for the treatment of COVID-19 was authorized by the American Food and Drug Administration (FDA) on April 3, 2020 but there are still many questions about optimal doses and treatments.

While the recommended duration of HCQ treatment (16), which was in available in the national treatment guidelines of our country since the first day of the disease appearance, was 5 days at the beginning of the pandemic, the treatment guidelines was updated on April 14, 2020 (17) with the extension of the treatment period to 10 days in ingravescent cases under HCQ treatment.

This retrospective, observational, single-center study aimed to reveal the effect of the duration of HCQ treatment on length of hospital stay, need for mechanical ventilation, duration of mechanical ventilation support, survival and cost in patients who were followed up at our hospital's intensive care unit for COVID-19. In this way, it is aimed to contribute to the determination of effective length of treatment and to prevent unnecessary therapies and hospitalization.

MATERIAL AND METHODS

Following the Ethics Committee approval (Protocol no: 2020/514/179/14, Date: 11/06/2020), the data of the patients who were followed up at Kartal Dr. Lütfi Kırdar City Hospital Coronavirus intensive care units with suspected or confirmed

Covid-19 and given HCQ therapy was retrospectively analyzed. After excluding the patients that met the exclusion criteria, 50 patients (Group 1) who completed 5-day HCQ treatment and the other 50 patients (Group 2) who completed 10-day HCQ treatment were enrolled in the study.

Exclusion criteria:

1- Patients who developed HCQ-related side effects and required drug discontinuation: QT prolongation, epileptic seizures, retinopathy, etc.

2- All patients who were able to complete the planned 5-day or 10-day HCQ therapy due to causes such as death and discharge

3- Patients receiving anti-cytokine therapy and immune plasma therapy besides the standard treatment regimen

4- Patients with missing data

Covid-19 diagnosis: Nasal and oral swab samples were taken from patients who applied to the emergency room or outpatient pandemic clinics with complaints including fever, fatigue, cough, chest pain, or diarrhea, and the Polymerase Chain Reaction (PCR) test was studied. Simultaneous low-dose chest computed tomography (CT) was performed on all patients presenting with these complaints, and lungs were scanned. Peripherally located, extensive patchy areas of pure ground glass opacities in bilateral lobular style were considered as characteristic chest CT findings of COVID-19 pneumonia. Positive PCR test confirmed Covid-19 diagnosis. In patients whose PCR was negative, in the presence of possible findings suggesting viral pneumonia in CT of the thorax, those patients were followed up with a probable diagnosis of Covid-19. In case of need for intensive care, these patients were admitted to the Covid-19 intensive care unit.

Standard treatment regimen other than hydroxychloroquine treatment: All patients who needed intensive care due to Covid-19 and had signs of pneumonia were administered 1600 mg loading dose of favipiravir followed by maintenance therapy of 400 mg twice daily for 5 days + 500 mg loading dose of AZ followed by maintenance therapy of 250 mg daily for 5 days. In addition to these therapies, all patients without contraindications received HCQ per day under ECG monitoring. HCQ protocol was determined as a loading dose of 800 mg followed by maintenance therapy of 200 mg daily for 5 or 10 days.

Data: Through retrospective analysis, subsequent patients' data including age, gender, presence of additional disease, Covid-19 PCR test results, HCQ treatment length, invasive mechanical ventilator (IMV) requirement and IMV duration, length of intensive care, mortality and treatment costs was recorded.

Group 1 (50 patients completing 5-day treatment) and Group 2 (50 patients completing 10-day treatment) were compared regarding their demographic data, IMV requirement and duration, length of stay at intensive care unit, mortality and treatment costs.

Statistical Analysis

Statistical software package (SPSS 21 Inc., Chicago, IL, USA) was used for biostatistical analysis. The data obtained from the patients participating in the study were expressed as mean, standard deviation and in percentages where appropriate. The distribution of the data was checked by the Kolmogorov-Smirnov test. Parametric data was compared between two independent groups using the One-way Anova test. Nonparametric tests were performed using the Kruskal-Wallis H test. Categorical groups were compared with the Chi-square test.

RESULTS

Since the admission of the first patient to the intensive care unit on 23 March 2020, 456 patients with Covid-19 have been followed up at our clinic during the pandemic. Until April 14, 2020 when the treatment algorithm changed, 272 patients were scheduled for 5-day HCQ treatment. From April 11, 2020 to June 15, 2020, 184 patients were scheduled for 10-day HCQ treatment. Among those patients, the first 50 patients who completed the 5-day therapy and the other 50 patients who completed the 10-day therapy were included in the study.

The average age of the study population was 69.7 years with a statistically significant difference between Group 1 (66.3 years) and Group 2 (73.1 years) (p=0.006). Male patients accounted for 61% of study population and there was no significant difference between the groups. The two groups were

similar in terms of comorbidities and the most common disease was hypertension. Table 1 shows the demographics of the patients.

Table 1: Demographic datas of patients

	Group 1 (n:50)	Group 2 (n:50)	General (n:100)	P
Age	66,3	73,1	69,73	0,00[a]
Gender				
Female	16 (%32)	23 (%46)	39 (%39)	0,10[b]
Male	34 (%68)	27 (%54)	61 (%61)	
Comorbidities				
No	11 (%22)	8 (%16)	19 (%19)	0.31[b]
Yes (At leastone)	39 (%78)	42 (%84)	81 (%81)	
DM	12 (%24)	17 (%34)	29 (%29)	
HT	27 (%54)	29 (%58)	56 (%56)	
CAD/CHF	15 (%30)	10(%20)	25 (%25)	
CRF	1 (%2)	3 (%6)	4 (%4)	
COPD	5 (%10)	11 (%22)	16 (%16)	
Malignity	3 (%6)	8 (%16)	11 (%11)	

[a]Oneway Anova, [b]PearsonChi-Square

DM: Diabetes Mellitus, HT: Hypertension, CAD:Coronary Artery Disease, CHF:Chronic Heart Failure,CRF: Chronic Renal Failure, COPD: Chronic Obstructive Pulmonary Disease.

Table 2 shows PCR test results, IMV requirement, ventilation time, mortality rates and cost analyses. According to the PCR test results, 52% of the patients had positive results and got confirmed Covid-19 diagnosis while 48% of the patients had negative results and got probable diagnosis. PCR positivity rate was higher in patients in group 1 (64% and 40% respectively; p=0.014).

Table 2: Clinical datas and cost analysis of groups

	Group 1 (n:50)	Group2 (n:50)	Total	p
PCR testing				
(+)	32 (%64)	20 (%40)	52 (%52)	0,014[a]
(-)	18 (%36)	30 (%60)	48 (%48)	
Length of ICU stay (day)	9,4	13,8	11,6	0,000[b]
IMV support				
(+)	39 (%78)	37 (%74)	76 (%76)	0,408[a]
(-)	11 (%22)	13 (%26)	24 (%24)	
IMV support time (hour)	200,9	196,7	198,9	0,861[b]
ICU Mortality (n,%)	34 (%68)	31 (%62)	65 (%65)	0,338[a]
Costanalysis ($)	3.368,78	4.840,67	4.104,72	0,002[b]

[a]Pearson Chi-Square, [b]Oneway Anova

PCR: Polymerase Chain Reaction, **ICU:** Intensive Care Unit, **IMV:** Invasive Mechanical Ventilator.

The need for mechanical ventilator was 76% in the entire study population, 78% in Group 1 and 74% in Group 2 (p=0.408) Mechanical ventilation duration was similar between the groups. The median length of stay in the intensive care unit was 11.6 days in the entire patient group. The length of stay at intensive care unit was longer in patients in Group 2 than in Group 1 (9.4 days vs. 13.8 days, p=0 <0001).

The mortality rate of the entire study population was 65% and there was no significant difference between the groups (68% and 62% respectively; p=0.338). When the intensive care hospitalization costs were compared between the two groups, it was found to be higher in Group 2 receiving 10-day therapy (Table 2).

PCR test positivity differed between the groups but there was no statistically significant difference between PCR positive and negative patients in terms of IMV requirement and duration, length of intensive care stay and mortality rates (Table 3).

Table 3: Clinical datas according to PCR positivity

	PCR (+) (n:52)	PCR (-) (n:48)	P
Length of ICU stay (day)	11,3	11,8	0,683[a]
IMV support			
(+)	39 (%75)	37 (%77,1)	0,497[b]
(-)	13 (%25)	11 (%22,9)	
IMV support time (hour)	217,3	179,5	0,117[a]
ICU Mortality (%)	67,3	62,5	0,384[b]

[a]Oneway Anova, [b]Pearson Chi-Square

PCR: Polymerase Chain Reaction, **ICU:** Intensive Care Unit, **IMV:** Invasive Mechanical Ventilator.

DISCUSSION

Comparing the results of two different patient groups who completed 5 or 10 days of HCQ therapy in intensive care, this retrospective observational study revealed that receiving 10-day treatment did not affect the need for mechanical ventilator and mortality despite significantly increasing the duration of hospitalization and the cost of intensive care.

At the time of the study, the spread of coronavirus in the world was close to 10 million confirmed cases and there were 192.000 cases in our country. Istanbul was the center of the pandemic in Turkey, and 516 patients were followed up in the intensive care at our site. The signs of COVID-19 infection may be mild, moderate and severe. Patients requiring follow-up in intensive care unit have severe disease, and may present with severe respiratory infection (severe pneumonia), Acute Respiratory Distress Syndrome (ARDS), sepsis, septic shock, myocarditis, arrhythmia and cardiogenic shock, and multiple organ failure. Some of the patients included in the study consisted of patients whose conditioned worsened while they

were already under treatment, and some consisted of patients who presented to the site with severe disease symptoms and were not under treatment yet.

Treatment protocols to be applied to patients admitted to intensive care were standardized through the guidelines prepared by our Ministry of Health and the National Science Board and have been developed with updates in line with current studies and available data. The first guidelines for treatment recommendation was released on March 16, 2020.

HCQ Treatment was among the recommended treatments as of the first guidelines.HCQ can cause a tendency for ventricular tachycardia by prolonging the QT interval. This risk is higher especially in elderly patients and those with cardiac comorbidities, using other drugs that prolong QT and with electrolyte disorders. For this reason, it is necessary to make a risk assessment for QT prolongation in patients who are starting or receiving HCQ due to COVID-19, and to make a decision by performing a cardiology consultation if necessary. Decision to continue treatment was made for our patients through daily ECG and QT monitoring, and patients who could not continue receiving treatment were excluded from the study. The statement "HCQ treatment can be extended up to 7-10 days in patients with fever or hypoxia despite a clinical response achieved at the end of the 5th day" entered the treatment protocol with the updated guidelines published on April 14, 2020. However, literature data on HCQ treatment is still unclear. Although there are specialists who support that HCQ is effective in the treatment of coronavirus, there are also others who argue that it is ineffective. There is still disagreement on its efficacy, effective dosage and duration of treatment.

The opinion that it is effective is mostly based on in vitro studies. The scientific letter written by a group of Chinese investigators examined the effect of CQ in vitro, using Vero E6 cells infected by SARS-CoV-2 at a multiplicity of infection (MOI) of 0.05.

That study indicated that CQ was highly effective in reducing viral replication, with an effective concentration (EC) 90 of 6.90 μM which can be easily achieved with standard dosing, due to its proper penetration in tissues including in the lung (18). Expert consensus on HCQ was published by a multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province on February 20th; however, no information was given about the method used for achieving consensus (19). Depending on in vitro evidence and nonpublished clinical experience, the panel recommended that patients diagnosed with mild, moderate and severe SARS-CoV-2 pneumonia be treated with 500 mg HCQ twice a day for 10 days.

The views in the systematic reviews depending on clinical experience are as follows: The Netherlands Centers for Disease Control and Prevention (CDC) suggested in public document on its website that serious infections be treated with chloroquine in patients who require admission to the hospital and oxygen therapy or need follow-up in the intensive care unit (20). The suggested regimen in adults is 600 mg CQ (6 tablets CQ 100 mg) followed by 300 mg after 12 hours on day 1, then 300 mg of CQ twice daily on days 2 to 5.

Another guideline document by the Italian Society of Infectious and Tropical Disease suggests the use of CQ 500 mg twice daily or HCQ 200 mg once daily for 10 days. The suggested target group ranged from patients with mild respiratory symptoms and comorbidities to patients with severe respiratory failure (21). On March 31, 2020, Chen et al. published results of a randomized parallel-group trial, where 62 hospitalized participants were randomized to receive either 400mg HCQ for five days in addition to standard of care or standard of care alone (22). The investigators reported that a more substantial proportion of those receiving HCQ had clinical improvement of pneumonia (80% vs. 55%, P<.04) as determined by chest CT. Four of the five HCQ studies shared the same dosing regimen (400 mg HCQ for five days). However, it has been reported based on in vitro data that doses as high as 800 mg or extended treatment with 400 mg for several days may be required for effective viral clearance in humans (23).

In a study (24) conducted in France, patients without contraindications were given a combination of 200 mg HCQ three times daily for ten days plus AZ (500 mg on day 1 followed by 250 mg daily for

the next four days). A total of 1061 patients (46.4% male, mean age 43.6 years (range from 14 to 95 years)) were included in this analysis, good clinical results and virological negativity were obtained in 973 (91.7%) patients within 10 days. Prolonged viral carriage was observed in 47 patients (4.4%) and was associated to a higher viral load at diagnosis (p<.001). A poor clinical outcome was observed in 46 patients (4.3%) and 8 (0.75%) patients aged from 74–95 years died. Our patients received both 5-day and 10-day HCQ treatments when they were being followed up at the intensive care unit as per the current treatment guidelines. However, there was no difference between patients who received 5-day therapy and those who received extended therapy regarding survival and need for IMV. The absence of any other research comparing different treatment durations in the literature is a unique feature of our study.

It has been reported that advanced age and the presence of concomitant diseases, especially chronic diseases such as hypertension (HT), diabetes mellitus (DM), chronic respiratory failure, are among the leading factors affecting mortality (25). The average age of patients in our study was similar to the literature data. Most of patients included in the study had at least one comorbid disease, HT being the most prevalent comorbid disease among our patients. Gender population was similar to data coming all over the world and males were dominant in the patient group.

Since PCR positivity differed between the patient groups, we investigated the effect of PCR positivity on survival, IMV requirement and IMV duration to obtain more homogeneous results and found that PCR positivity had no significant effect on these outcomes.

Intensive care costs of patients who received the treatment regimen extended to ten days were found to be significantly higher. In a study that reflects the virtual cost analysis conducted in the USA, the median value per person for patients followed up in the intensive care unit was be approximately 14.000 dollars (26). Despite extended hospitalization and increased costs, the median cost in our study was almost 4.000 dollars per patient. This resulted from the fact that Turkish health care system covers provision of detailed services and patients can freely and easily access to hospitals.

Limitations

One of the major limitations of this study is its retrospective design. There is a need for studies involving randomized, controlled, larger samples of patients followed up in the intensive care unit. Also, it was not possible to evaluate serum drug levels during intensive pandemic period. Conclusion

There is still no proven standard treatment regimen for patients requiring intensive care follow-up due to COVID-19. While preparing treatment guidelines, suggestions are presented in the light of current studies and reviews and it is concluded that HCQ treatment, which is extended to 10 days, is ineffective and it increases hospitalization and the cost of care.

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