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Compliance and feedback of hydroxychloroquine treatments in home follow-up patients with diagnosis of COVID-19

COVİD-19 tanısıyla evde takip edilen hastaların hidroksiklorokin tedavisine uyumları ve geri bildirimleri

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Öz

Giriş ve Amaç: Bu çalışmada Eğitim Aile Sağlığı Merkezlerine (EASM) kayıtlı ve COVID-19 nedeniyle evde hidroksiklorokin (HCQ) tedavisi alan hastaların ilaç uyumlarını ve geri bildirimlerinin değerlendirilmesi amaçlandı.
Gereç ve Yöntemler: Hastanemize bağlı Eğitim Aile Sağlığı Merkezlerinde kayıtlı COVID-19 nedeniyle evde tedavi gören ve HCQ tedavisi gören hastalar dahil edildi. Evde takip edilen bu hastalara ev takiplerinin 6. ve 14. günleri arasında bir kez ulaşıldı. Hastalara HCQ tedavisine uyumları, ilaç yan etkileri, geri bildirimler, ateş ve öksürük gibi semptomların süreleri, hastaneye yeniden sevklerle ilgili bilgileri içeren 31 maddeden oluşan anket soruları yöneltildi. Anket yoluyla toplanan veriler istatistiksel analiz ile değerlendirildi. İstatistiksel analizler SPSS 17.0 programı ile yapıldı.
Bulgular: Çalışmaya 37'si erkek 30'u kadın toplam 67 hasta katıldı. Ortalama yaş 45.34 ± 19.01 yıldır. Orta derecede semptomları olan 7 hasta ve hafif semptomları olan 60 hasta vardı. Bir hasta ilaca bağlı cilt döküntüsü nedeniyle tedaviyi bıraktı. 63 hastanın semptomlarında azalma oldu. Hastaneye yatan 23 hastanın ortalama yatış süresi 12.96 ± 5.92 gündü. Tekrar hastaneye sevk edilen 5 hasta vardı. Azitromisin kullanımı olanlarda tekrar hastaneye sevk oranı daha düşük bulundu.
Sonuç: HCQ kullanan evdeki takip edilen COVİD-19 hastalarının çoğunluğunun semptomlarında hafifleme olmuştur. HCQ ile kombine azitromisin tedavisi alanlarda tekrar hastaneye yatma oranları daha düşük gözlenmiştir.

Anahtar kelimeler: Azitromisin, COVİD-19, Hidroksiklorokin.

Abstract

Objective: In this study we aimed to evaluate the medication compliance and feedback of the patients who were registered in Education Family Health Centers (EASM) and who received hydroxychloroquine (HCQ) treatment at home due to COVID-19.
Materials and Methods: Patients who were being treated at home and being treated for hydroxychloroquine due to COVID-19 registered in Education Family Health Centers affiliated to our hospital were included. These patients who were followed at home were contacted once between the 6th and 14th days of home follow-up. The patients were asked questionnaire questions including 31 items including information on their compliance with hydroxychloroquine treatment, drug side effects, feedback, duration of symptoms such as fever and cough, re-referrals to the hospital. The data collected through questionnaires were evaluated by statistical analysis.
Results: Statistical analysis was done with SPSS version 17.0 program. A total of 67 patients, 37 men and 30 women, participated in the study. The average age is 45.34 ± 19.01 years. There are 7 patients with moderate symptoms and 60 people who have mild symptoms. One patient had skin rush and stopped the treatment because of adverse effect. 63 patients had a reduction in their symptoms. There were 23 patients hospitalized and the average duration is 12.96

± 5.92 days. There were 5 patients who are referred to the hospital again. Among patients 33 were receiving azithromycin combined with HCQ and their re-hospitalization rates were lower.
Conclusion: HCQ was observed efficient in relieving the COVİD-19 symptoms in most of the home follow-up patients Azithromycin combined with HCQ reduced re-hospitalization rates.

Keywords: Azithromycin, COVİD-19, Hydroxychloroquine.

1. Introduction

Hydroxychlororoquine (HCQ) has been used asdrug widely in prophylaxis and treatment of malaria for a long time [1]. Antimalarial drugs currently used for autoimmune diseases like rheumotoid arthritis (RA) [2b]. Antimalarial drugs have antiviral effects like reducing viral replication.HCQ could be used to treat viral enfections [1]. HCQ has been used against Ebola virüs, immun deficiency virüs (HIV), Middle East Respratory Syndrome (Mers-CoV) and SARS-CoV-2 [2]. It is reported patients with COVİD-19 pneumonia could be treated with 500 mg chloroquine twice aday for ten days [3].

HCQ is an analogue of chloroquine and have an antiviral activity against SARS-CoV in vitro [4].

Due to the COVID-19 pandemic that emerged and spread in the Wuhan Hubai region of China, patients with suspected COVID-19 contact or definite diagnosis who do not have an indication for hospitalization are followed at home by family health units. The symptoms, treatment and test results of the patients are monitored by their family physicians [3].

In our country hydroxychloroquine (HQ) treatments have been recommended by Public Health Directorate of Ministry of Health since the beginning of the pandemic in COVID-19 in Guidelines [5,6]. Although the use of favipiravir, one of the antiviral treatments, was started with the change of treatment protocols, the use of hydroxychloroquine was continued. Molnupiravir is another antiviral recommended for mild and moderate COVID-19 patients in 5 days of initiation of infection and at high risk for progression disease. With the increase in vaccination rates, the recommendations for drug use in mild cases have decreased [5,7].

HCQ treatment was started in probable or definite cases or cases with uncomplicated or mild pneumonia and these patients were followed up by family physicians at home. Oral HCQ 2x200 mg tablets were used for 5 days in uncomplicated possible or definite cases, and 2x200 mg oral tablet was used for 5 days following a 2x400 loading dose in cases with possible or definite diagnosis of mild pneumonia [6].

In this study we aimed to evaluate the medication compliance and feedback of the patients who were registered in Education Family Health Centers (EASM) and who received hydroxychloroquine treatment at home due to COVID-19.

2. Materials and Methods

2.1. Study Design

The data of patients with a diagnosis, suspicion or contact of COVID-19 and who need to be followed at home are sent to the family health units where they are registered by the public health directorate. An observational study was planned to question the patients' compliance with hydroxychloroquine treatment and their feedback. Patients over the age of 18 who were being treated at home and being treated for hydroxychloroquine due to COVID-19 registered in Sisli and Hurriyet Education Family Health Centers affiliated to Cemil Tascıoglu City Hospital were included.

2.2. Sample Universe

Patients over the age of 18 who were being treated at home and being treated for hydroxychloroquine due to COVID-19 registered in Sisli and Hurriyet Education Family Health Centers affiliated to Cemil Tascıoglu City Hospital were included. Survey data were collected by the researchers by contacting these patients by phone. Our study lasted 15 days and was conducted between 05-20 September 2020. Number of patients followed at home due to COVID-19 registered in Sisli and Hurriyet Education Family Health Centers were 72. HCQ treatment was given to all 72 patients. Five patients were not included in the study because they could not be reached by phone and information could not be obtained. These patients who were followed at home were contacted by phone, once between the 6th and 14th days of home follow-up, after the 5th day of the completion of hydroxychloroquine treatment. All of these 67 patients agreed to participate.

2.3. Data Collection

Patients informed about the study and their consent was obtained. Survey questions containing 31 items including information on their compliance with hydroxychloroquine treatment, drug side effects, feedback, duration of symptoms such as fever and cough, re-referrals to the hospital, length of hospitalization and sociodemographic information, asked to the patients who accepted to participate in the study by a questionnaire.

2.4. Statistical Analysis

The data collected through questionnaires were evaluated by statistical analysis. IBM SPSS Statistics 17 for statistical analysis (SPSS IBM, Turkey) program was used. While evaluating the study data, besides descriptive statistical methods (mean, standard deviation, frequency), the Chi-Square test was used to compare qualitative data and Student's t test was used to compare quantitative data. Significance was evaluated at the $p < 0.05$ level.

Statistical analysis was done with SPSS version 17.0 program. The compliance of the variables to normal distribution was examined using histogram graphics and Kolmogorov-Smirnov test. Mean, standard deviation, and median values were used while presenting descriptive analyzes. Categorical variables were compared using the Pearson Chi-Square Test. Mann Whitney U Test was used to evaluate nonparametric

variables between the two groups. The situations where the p-value was less than 0.05 were evaluated as statistically significant results.

2.5. Ethics

Ethics committee approval for the study was obtained from the Ethics Committee of Prof. Dr. Cemil Tascıoglu City Hospital on date August 25, 2020 and number 139. Written permission has also been obtained from the Turkish Medicines and Medical Devices Agency, with the guidance of the Ethics Committee, as it is a study in which the drug effect is observed.

3. Results and Discussion

3.1.Results

A total of 67 patients, 37 men and 30 women, participated in the study. The average age is 45.34 ± 19.01 years. The average age of males was 44.43 ± 18.62 years, while the average age of females is 46.47 ± 19.74 years. There are 7 patients with moderate symptoms and 60 people who have mild symptoms shown in Table 1.

Table 1. Age and gender of participants

		n/medium±s.d.	**%/Median**
Age		45.34±19.01	40.00
Male age		44.43±18.62	38.00
Female age		46.47±19.74	41.00
Age	≤39	33	(49.25)
	40-49	10	(14.93)
	50-59	10	(14.93)
	60-69	5	(7.46)
	≥70	9	(13.43)
Gender	Male	37	(55.22)
	Female	30	(44.78)
Symtoms	Moderate	7	(10.45)
	Mild	60	(89.55)

There were 26 patients with additional chronic diseases and 20 patients with regular medication. There were 11 smokers. The average annual consumption of smokers is 7.77 ± 5.36 packs. Among patients 33 were receiving azithromycin combined with HCQ. There were 10 patients receiving enoxaparin sodium, 2 patients receiving oseltamivir phosphate, 2 patients receiving favipiravir and 7 patients receiving acetylcysteine with ascorbic acid (vitamin C). There were 12 patients still taking medication.

All the listed symptoms were seen as the initial symptoms. There were 8 patients with newly developed symptoms after medication. Fever, cough, shortness of breath, joint pain, runny nose, nasal congestion were noted as later symptoms. One patient had skin rush and stopped the treatment because of adverse effect.

There were 37 patients with fever and fever lasted for an average of 3.92 ± 1.89 days. There were 39 patients with cough and it took an average of 9.51 ± 7.74 days. There were 20 patients with shortness of breath and it took an average of 6.00 ± 2.96 days. There were 23 patients hospitalized and the average duration is 12.96 ± 5.92 days. There were 5 patients who are referred to the hospital again. 3 patients have had the flu vaccine (Table 2 and Table 3).

Hospitalization, age, gender, comorbid chronic diseases and symptoms were compared. The average age of those hospitalized is higher than those who are not hospitalized. The rate of those who are 70 years and over hospitalizedis higher than those who are not hospitalized. The rate of fever and shortness of breath in hospitalized patients is higher than those who are not hospitalized shown in Table 4.

Re-hospitalization rates were lower in azithromycine combined with HCQ group. There were not a statically significant difference in duriation of symptoms in HCQ alone and azithromycine combined with HCQ group shown in Table 5.

Table 2. Numbers and percentages of characteristics of patients

	n	%
Patients having a chronic disease	26	(38.81)
Patients who constantly used medication	20	(29.85)
Smokers	11	(16.42)
Has any other medicine been given except HCQ?	51	(76,12)
Azithromyçin	33	(64.71)
Enoxaparin sodium	10	(19.61)
Oseltamivir phosphate	6	(11.76)
Favipiravir	2	(3.92)
Acetylcysteine with ascorbic acid	7	(13.73)
Inability of adherence to the treatment plan	0	(0.00)
Is he still taking the medicine?	12	(17.91)
New symptoms after medication	8	(11.94)
Adverse effects	1	(1.49)
Stop the treatment halfway because of adverse effects	1	(1.49)
Stop the treatment because the COVİD-19 symptoms are under control?	0	(0.00)
Fever	37	(55.22)
Cough	39	(58.21)
Shortness of breath	20	(29.85)
Diarrhea and abdominal pain	10	(14.93)
Joint pain	24	(35.82)
Runny nose	3	(4.48)
Nasal congestion	6	(8.96)
Anosmia	3	(4.48)
Reduction in symptoms	63	(94.03)
Hospitalized	23	(34.33)
Re-hospitalization	5	(7.46)
Have you had a flu vaccine?	3	(4.48)

Table 3. Mean values of some parameters about patients

	Mean±s.d.	Median
Cigarette pack / year	7.77±5.36	7.00
Day of follow-up at home	8.78±4.67	10.00
How many days ago contact with a COVİD-19 case	11,97±7.24	10.00
Day of medication	3.55±1.51	4.00
If the medicine is over, how many days has it been	9.18±7.13	8.00
How many days did the fever last?	3.92±1.89	3.00
How many days did the cough last?	9.51±7.74	7.00
How many days did the shortness of breath last?	6.00±2.96	5.00
How many days did diarrhea and abdominal pain last?	4.09±3.11	3.00
How many days did joint pain last?	5.48±3.58	5.00
Duration of hospitalization in hospitalized patients	12.96±5.92	12.00

Tablo 4. Comparison of non-hospitalized and hospitalized patients

		Non- hospitalized		**Hospitalized**		**p[1]**
		n	**%**	**n**	**%**	
Age		39.77±16.23	37.00	56.00±19.70	55.00	**0.001[2]**
Age groups	≤39	28	(63.64)	5	(21.74)	**0.016**
	40-49	6	(13.64)	4	(17.39)	
	50-59	5	(11.36)	5	(21.74)	
	60-69	2	(4.55)	3	(13.04)	
	≥70	3	(6.82)	6	(26.09)	
Gender	Male	25	(56.82)	12	(52.17)	0.717
	Female	19	(43.18)	11	(47.83)	
Chronic disease		14	(31.82)	12	(52.17)	0.104
Fever		20	(45.45)	17	(73.91)	**0.026**
Cough		25	(56.82)	14	(60.87)	0.750
Shortness of breath		7	(15.91)	13	(56.52)	**0.001**
Diarrhea anad abdominal pain		6	(13.64)	4	(17.39)	0.682
Joint pain		13	(29.55)	11	(47.83)	0.138
Runny nose		3	(6.82)	0	(0.00)	0.200
Nasal congesion		6	(13.64)	0	(0.00)	0.063
Anosmia		3	(6.82)	0	(0.00)	0.200

[1]Chi- square Test [2]Mann Whitney U Test

Table 5. Comparison of HCQ treatment and azithromycin with HCQ combined treatment group

	HCQ		**HCQ+Azithromycine**		**p**
	n	**%/median**	**n**	**%/median**	
Fever	9	(50,00)	21	(63,64)	0,344
How many days did the fever last?	3,78±1,20	4,00	4,14±2,03	4,00	0,782[2]
Cough	9	(50,00)	22	(66,67)	0,244
How many days did the cough last?	6,60±5,10	6,00	12,33±8,83	9,00	0,065[2]
Shortness of breath	6	(33,33)	10	(30,30)	0,824
How many days did the shortness of breath last?	4,83±1,33	5,00	7,11±3,14	7,00	0,079[2]
Diarrhea and abdominal pain	4	(22,22)	4	(12,12)	0,343
How many days did the diarrhea and abdominal pain last?	3,00±1,41	2,50	6,50±4,20	6,00	0,180[2]
Joint pain	10	(55,56)	9	(27,27)	**0,046**
How many days did the joint pain last?	5,70±1,89	5,00	6,33±5,43	5,00	0,590[2]
Reduction in symptoms	17	(94,44)	32	(96,97)	0,657
Hospitalized	11	(61,11)	11	(33,33)	0,056
Duration of hospitalization	12,73±7,27	10,00	13,36±4,86	15,00	0,427[2]
Re-hospitalization	4	(22,22)	1	(3,03)	**0,028**

[1]Chi- square Test [2]Mann Whitney U Test

3.2.Discussion

Chloroquin (CQ) have been frequently used in the treatment of systemic lupus erythematosus (SLE) and other rheumatismal diseases as immun system regulator [1,2]. HCQ antiviral activity has been proven including human coronavirus [1]. Prophylactic and therapeutic effects of HCQ for SARS-CoV infection were reported [15].

In China guides for COVID-19 have also reported chloroquine phosphate superior to the CQ in treatment of SARS-CoV-2 infection [16,17]. A study evaluated the efficacy of hydroxychloroquine HCQ (the sulfate and phosphate salts of CQ) in the treatment of COVID-19. In this patients after 5 days of HCQ treatment, the symptoms were significantly reducted and in the recovery times for cough and fever were shorten.

In a retrospective observational study to investigate the relationship between HCQ therapy and COVID-19 in-hospital mortality it is reported that HCQ use was associated with a 30% lower risk of death in COVID-19 hospitalized patients due to COVİD-19 [6].

Studies emphasize that approximately 81% of patients with COVID-19 show only mild symptoms and do not require hospitalization [18, 19]. There are very few studies investigating the course of the disease in mild cases. A research reported symptoms were generally described as mild sore throat, cough, and mild fever, and they were observed to begin to appear on the third day. Also in this research symptoms disappeared on the 10th day after the PCR test positivity was detected. However, it was observed that the polymerase chain reaction test could be tested positive until the 21st day [20]. In our study 60 (89.55%) patients have mild symtoms, 7(10.45%) have moderate symptoms and There were 63(94.3%) patients has a reduction in symptoms, 8 (11.94%) patients had new new symptoms after medication 23 (34.33%) patients were hospitalized, 5 patients were (7.46%) re-hospitalized.

In astudy conducted to evaluate the efficacy of hydroxychloroquine (HCQ) in the treatment of patients with COVID-19 fever and the cough symptoms remission time were significantly shortened in the patients HCQ treatment was used. In patients with COVID-19, the use of HCQ could significantly shorten clinical recovery time and promote the recovery of pneumonia. For fever, 17 patients in the control group and 22 patients in the HCQ treatment group had fever. HCQ treatment group had duration of fever (2.2±0.4 days) was shorter when compared with the control group (3.2± 1.3 days) [24]. In our study there were 37 patients with fever and it lasted for an average of 3.92 ± 1.89 days. There were 39 patients with cough and it took an average of 9.51 ± 7.74 days.

HCQ is a safe immunomodulatory agent for rheumatic diseases. Rare adverse effects like Corrected QT (QTc) interval prolongation, cardiomyopathy, retinopathy, have been observed [2]. In present study there were 2 patients with mild adverse reactions in the HCQ treatment group among 31 patients who received an 5-day HCQ (400 mg/d) treatment there were two patients with mild adverse reactions in the HCQ treatment group, one patient developed a rash, and one patient had a headache, none severe side effects appeared among them [24]. In our study one patient gave up medication in second day because of skin rush.

In an observational study, analysis with a large sample of patients who had been hospitalized with Covid-19, the risk of intubation or death was not significantly higher or lower among patients who admited hydroxychloroquine than among those who did not [25].

It is shown in a study HCQ is clearing viral load of SARS-CoV-2 in nasopharyx in about three to six days and azithromycin with hydroxychloroquine was prominently more efficient for virus elimination [26]. They also showed in another clinical study of 80 COVID-19 patients that HCQ combined with azitromisin reduce nasopharyngeal viral load significantly (83%) negative at Day 7, and 93% at Day 8 tested by RT-PCR [27]. Also in a study it is reported Chloroquine limits the replication of SARS-CoV-2 [28].

Some retrospective cohort analyses reported no efficacy of HCQ in virological clearance of COVID-19 [2]. Mitjà at al. reported no significant differences in the mean reduction of viral load at day 3 or at day 7. HCQ treatment did not reduce risk of hospitalization and did not shortened the time to complete resolution of symptoms. No relevant treatment-related advers affects were reported [1].

A study in patients with mild to moderate COVID-19 disease at high risk of worsening, reported that patients who treated with HCQ did not have better clinical or virological outcomes than those receiving placebo [4].

Among patients hospitalized in New York metropolitan region with COVID-19 receiving HCQ alone, azithromycin alone, or combination of HCQ and azitromycin, compared with neither treatment, were not significantly effective on hospital mortality [29].

A study conducted to investigate the role of HCQ therapy alone and in combination with azithromycin in hospitalized patients positive for COVID-19 with median time to follow-up of 28.5 days was associated with reduction in mortality.hospital mortality was 13.5% in the hydroxychloroquine alone group, 20.1% in hydroxychloroquine + azithromycin combined group, 22.4% in azithromycin alone group, and 26.4% in receiving neither drug group. Primary cause of mortality was 88% respiratory failure, 4% cardiac arrest (with mean QTc interval from last ECG reading 471 ms), 8% other cardiopulmonary arrest and multi-organ failure. No patient had reported torsades de pointes. treatment with hydroxychloroquine alone decreased the mortality hazard ratio by 66% , and hydroxychloroquine + azithromycin combination decreased the mortality hazard ratio by 71% ($p < 0.001$) [30]. In our study 33 patients recieved azithromycin with HCQ. Azithromycin combined with HCQ treatment group patients had lower re-hospitalizasyon rates than HCQ alone treatment group.

Although HCQ is one of the first drugs used in the treatment of COVID-19, its effectiveness in treatment

has not been sufficiently proven. The side effects of HCQ have also limited its use, and it is not currently recommended for the treatment of COVID-19 outside of clinical use under strict medical supervision. Its use in combination with other drugs has also become limited due to cardiac conduction disorders and corrected QT (QTc) interval prolongation [2].

This study has several limitations. The data collected in a limited time period and the data were taken from the daily follow-up records of the patients.

4. Conclusion

HCQ was observed efficent in relieving the COVİD-19 symptoms in most of the home follow-up patients. It was observed that 94 % of the patients had regression in symptoms. Treatment with azithromycin combined with HCQ was lowering re-hospitalizasyon rates. Use of HCQ in COVID-19 patients currently not encouraged outside clinical trials under strict medical supervision because of severe life-threatening adverse effects. Clinical trials with large number of patient groups could give more accurate results.

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