Review Article

The Effect of Hydroxychloroquine on Mortality and Pneumonia Development in SARS-Cov-2 Positive Mildly Symptomatic Outpatients without Findings of Pneumonia

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Abstract

Although a period longer than 10 months has passed since the detection of the first cases in and more than 40 million people have been diagnosed with COVID-19 worldwide, there is still no well-accepted and proven treatment choice for the novel coronavirus disease. This study aimed to retrospectively investigate cases in whom treatment had started due to detected as positive during screening and also having shown signs including fever, cough, shortness of breath, excessive malaise, fatigue or loss of smell-taste, without any findings of pneumonia between March 11, 2020, when the first cases were detected in Turkey, and the beginning of May, 2020.

A total of 19.276 SARS-CoV-2 PCR positive outpatients, within the first 48 hours of detection and had no findings in lung auscultation or radiology, were detected from the data of Health Information System. 9559 patients were males (49.6%) and 9717 were females (50.4%). An underlying disease considered in the risk group for COVID-19 was found in 1789 of the patients (8.8%). An underlying disease was present in 9.4% using hydroxychloroquine and in 9% not using hydroxychloroquine. 43 deaths (0.2%) were detected among all cases. Mortality in cases using and not using hydroxychloroquine was respectively 5 (in 12.293 cases) and 38 (in 6.983 cases).

It was confirmed that pneumonia developed in 2.080 of the patients (10.8%). This number was found as 1286 (10.5%) in cases using HQ and as 794 (11.4%) in cases not using HQ. In conclusion, since this study confirmed that hydroxychloroquine used in outpatients presenting in the early period without any symptoms of pneumonia can ensure survival and prevent pneumonia development particularly in young adults, we may speculate that the early use of hydroxychloroquine in mildly symptomatic patients results in a cost-effective and potent treatment.

Keywords: COVID-19; SARS-CoV-2; Treatment; Hydroxychloroquine

Introduction

The signs of COVID-19 pandemic started to emerge in the city of Wuhan in China with patients who presented with symptoms of viral respiratory tract infection and in whom no agent could be detected in December 2019. A short time after the evaluation of the first cases and detecting that these cases were associated with a live animal market, the agent was confirmed to be a coronavirus and was documented to possess similarities with another coronavirus, namely SARS-CoV, detected as an agent in 2002. A specific antiviral treatment has not been found against the coronaviruses causing SARS and MERS that became widely known in the 2000s and those showing seasonal prominence or being dominantly seen in the childhood period [1-3].

Discovered first in the 1930s, chloroquine has been widely used in malaria (for protection and treatment purposes) and in autoimmune disease like rheumatoid arthritis and systemic lupus erythematosus [4-7]. Its antecedent, an herbal form, had been used by the South American Natives centuries ago. Following the realization that this herbal powder obtained from the bark of the tree referred to as Cinchona was effective in malaria, it was brought to Europe in the seventeenth century, and this form had been used in the treatment of malaria for a very long time. In the meantime, it was discovered coincidentally that the powder was also useful in rheumatoid arthritis and systemic lupus erythematosus and could be used in treatment. Thanks to the studies, continuing after the Second World War hydroxychloroquine was produced following its modification through hydroxylation. Hydroxychloroquine is now preferred more due to the fact that it has similar effect and indication spectrum but less side-effect frequency [7]. Hydroxychloroquine reaches its peak plasma concentration in 3-4 hours, and chloroquine reaches the same concentration in half an hour [8,9]. Half-life of chloroquine and hydroxychloroquine is long, they can remain in the body for days and even weeks, and urinary excretion may continue up to 3 months [10,11].

There are a limited number of studies on the antiviral activity of chloroquine and hydroxychloroquine, and they were started to be used experimentally in the SARS-CoV-2 pandemic since it had already been established to have *in-vitro* activity in the epidemics caused by SARS-CoV-1 and MERS CoV [12-15]. It is considered that chloroquine and hydroxychloroquine have more than one effect mechanism on SARS-CoV-2. Their first effect is blocking the cellular ingestion of the host cell receptor, Angiotensin Converting Enzyme 2 (ACE2), by inhibiting its glycosylation [15-17]. Second, chloroquine and hydroxychloroquine disrupt the stability of intracellular pH and organelles by penetrating into endosome and lysosome and prevents the reproduction of the virus within the cell and infection by suspending protein catabolism, endocytosis, and exocytosis necessary for the replication and infection of the virus [18]. It has also been proven by previous studies that the anti-inflammatory and immune-modulator effects of these drugs increase antiviral activity *in-vivo* [19]. In studies conducted for the *in-vitro* activity of chloroquine, it has been shown that chloroquine and hydroxychloroquine are extremely effective in decreasing viral replication and could easily reach EC_{50} (50% of maximum-effective concentration) level with standard dosage [15,16,20]. EC_{50} level of chloroquine at the 48th hour showing *in vitro* activity against SARS-CoV-2 in Vero E6 cells has been determined as $1.13\mu M$ [16]. While the infection degree of chloroquine and hydroxychloroquine in Vero E6 cells was 0.01, their level of activity against SARS-CoV-2 was found respectively as EC_{50} $2.71\mu M$ and $4.51\mu M$ [16]. Moreover, their antiviral activities increase thanks to the well-spread of these agents to tissues, and more specifically the lungs [15]. While chloroquine has been found more effective *in vitro* against the SARS-CoV-1 infection in previous studies, hydroxychloroquine has been proven to be more effective in studies conducted on the SARS-CoV-2 infection [15,21].

The first case in Turkey was confirmed in March 11, 2020, and the Coronavirus Scientific Advisory Board formed by the Ministry of Health published a diagnostic, treatment, and follow-up protocol upon its detection and was started to be used widely in the country. Within this framework, it was aimed to evaluate the possible effects of hydroxychloroquine by retrospectively analyzing the data of the patients followed until the second week of April 2020.

Materials and Methods

Primary healthcare is provided and followed by family practitioners in Turkey. Healthcare institutions with beds are comprised of those of the Ministry of Health, universities, private institutions, and foundations. Majority of the healthcare services are given by the state and a healthcare insurance system covering all citizens is enforced. As of the onset of the pandemic, all drugs used in inpatient and outpatient clinics in all treatment facilities have been offered free of charge by the Ministry of Health. Recommendations for treatment have been implemented pursuant to the COVID-19 (SARS-CoV-2 Infection) Guideline comprising all case evaluation and treatment recommendations published by the Coronavirus Advisory Board of the Ministry of Health of Turkey. Within this perspective, this study retrospectively investigated cases in whom treatment had swiftly started due to having being evaluated as having had contact, detected as positive during screening and also having shown signs including fever, cough, shortness of breath, excessive malaise, fatigue
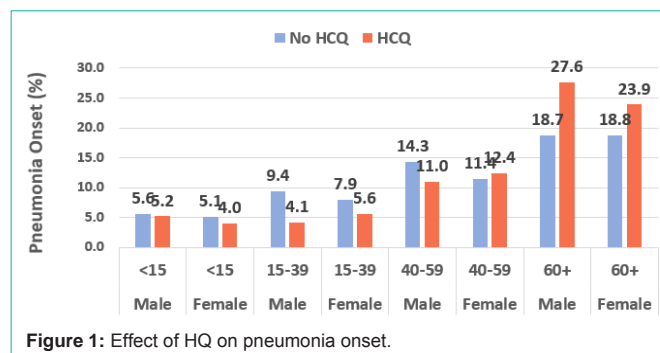

Figure 1: Effect of HQ on pneumonia onset.

or loss of smell-taste, but not any findings of pneumonia between March 11, 2020, when the first cases were detected in Turkey, and the beginning of May, 2020.

In terms of case evaluation, mortality and pneumonia development were chosen as the main criteria, and 30-day survival and development of adverse effects were also discussed. In order to have a detailed distribution of age groups evaluating symptoms and course of the disease, the patients were grouped as 0-1 year, 2-11 years, 12-14 years, 15-18 years, 19-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, and 70 years and older. A secondary grouping was made for mortality evaluation and pneumonia development as follows: 15 years and younger, 15-39 years, 40-59 years, and 60 years and older. Patient records were accepted according to the physician's notes, who examined and noted down patient's history. When symptoms were investigated in the records, fever was confirmed upon measuring a temperature of 38ºC and higher with contact-free thermometer in all patients. Furthermore, the records were scanned for the presence of cough, shortness of breath, loss of taste-smell, headache, malaise, muscle pain, and diarrhea, and whether these symptoms developed following the first positivity detection or not.

Since the use of hydroxychloroquine is recommended as 2x200 mg for 5 days pursuant to the Ministry of Health COVID-19 Guideline, all cases using hydroxychloroquine were evaluated as having received this dosage accordingly. In the follow-up of the cases, information regarding the presence of pneumonia development within the 14 days following PCR positivity was extracted from follow-up and medical records. Similarly, mortality until the 30th day of PCR positivity was also scrutinized.

Results

A total of 19.276 SARS-CoV-2 PCR positive outpatients, who were confirmed during filiation (contact tracing) and presented with no complications or were within the first 48 hours of complications and who had no findings in lung auscultation or radiology, were detected from the data of Health Information System. Nine thousand five hundred and fifty-nine patients were males (49.6%) and 9717 were females (50.4%). Other demographic data are presented in (Table 1).

In terms of underlying diseases, an underlying disease considered in the risk group for COVID-19 was found in 1789 of the patients (8.8%). An underlying disease was present in 1161 patients (9.4%) using Hydroxychloroquine (HQ) and in 628 patients (9%) not using hydroxychloroquine. The distribution of underlying diseases

Table 1: Distribution of the age groups.

Age group	Number			Sex		Hydroxychloroquine Use	
	Number (n)	Percentage (%)	Cumulative Percentage (%)	Male n (%⁻)	Female n (%*)	No n (%*)	Yes n (%*)
0 month-1 year	75	0.4	0.4	34 (45.3)	41 (54.7)	41 (54.7)	34 (45.3)
2-11 years	805	4.2	4.6	410 (50.9)	395 (49.1)	335 (41.6)	470 (58.4)
12–14 years	411	2.1	6.7	210 (51.1)	201 (48.9)	141 (34.3)	270 (65.7)
15-18 years	648	3.4	10.1	317 (48.9)	331 (51.1)	202 (31.2)	446 (68.8)
19-29 years	3835	19.9	30	1895 (49.4)	1940 (50.6)	1380 (36.0)	2455 (64.0)
30-39 years	4074	21.1	51.1	2068 (50.8)	2006 (49.2)	1443 (35.4)	2631 (64.6)
40-49 years	3550	18.4	69.5	1765 (49.7)	1785 (50.3)	1299 (36.6)	2251 (63.4)
50-59 years	2778	14.4	83.9	1362 (49.0)	1416 (51.0)	1048 (37.7)	1730 (62.3)
60-69 years	1964	10.2	94.1	983 (50.1)	981 (49.9)	714 (36.4)	1250 (63.6)
70 years and older	1136	5.9	100	515 (45.3)	621 (54.7)	380 (33.5)	756 (66.5)

⁻Row Percentage.

Table 2: 14-day mortality by age group, gender, comorbidity and HCQ use in COVID-19 patients monitorized with home care.

				Male			Female			All Patients		
				Deaths	% Dead	Total N	Deaths	% Dead	Total N	Deaths	% Dead	Total N
Age Group	<15	Hydroxychloroquine Use	Absent	0	0.00%	269	0	0.00%	294	0	0.00%	563
			Present	0	0.00%	460	0	0.00%	424	0	0.00%	884
			Total	0	0.00%	729	0	0.00%	718	0	0.00%	1447
	15-39	Hydroxychloroquine Use	Absent	0	0.00%	1494	1	0.10%	1485	1	0.00%	2979
			Present	0	0.00%	2711	0	0.00%	2711	0	0.00%	5422
			Total	0	0.00%	4205	1	0.00%	4196	1	0.00%	8401
	40-59	Hydroxychloroquine Use	Absent	2	0.20%	1159	2	0.20%	1188	4	0.20%	2347
			Present	0	0.00%	1968	0	0.00%	2013	0	0.00%	3981
			Total	2	0.10%	3127	2	0.10%	3201	4	0.10%	6328
	60⁺	Hydroxychloroquine Use	Absent	21	4.00%	524	12	2.10%	570	33	3.00%	1094
			Present	2	0.20%	974	3	0.30%	1032	5	0.20%	2006
			Total	23	1.50%	1498	15	0.90%	1602	38	1.20%	3100
	All ages	Hydroxychloroquine Use	Absent	23	0.70%	3446	15	0.40%	3537	38	0.50%	6983
			Present	2	0.00%	6113	3	0.00%	6180	5	0.00%	12293
			Total	25	0.30%	9559	18	0.20%	9717	43	0.20%	19276
Comorbidity	Absent			19	0.20%	8854	12	0.10%	8633	31	0.20%	17487
	Present			6	0.90%	705	6	0.60%	1084	12	0.70%	1789
All Patients				25	0.30%	9559	18	0.20%	9717	43	0.20%	19276

in the whole group and in the patients who used and did not use hydroxychloroquine was found respectively as follows: diabetes mellitus (DM) 476 (2.5%), 330 (2.7%), 146 (2.1%), hypertension 748 (3.9%), 502 (4.1%), 246 (3.5%), asthma 872 (4.5%), 544 (4.4%), 328 (4.7%), chronic renal failure 17 (0.1%), 11 (0.1%), 6 (0.1%), and cancer 66 (0.3%), 41 (0.3%) 25 (0.4%).

In terms of hydroxychloroquine use, it was found that 12.293 (63.8%) patients used hydroxychloroquine. In terms of mortality, 43 deaths (0.2%) were detected among all cases. Mortality in cases using and not using hydroxychloroquine was established respectively as 5 (in 12.293 cases) and 38 (in 6.983 cases, 0.5%). The age groups in which mortality occurred were as follows: one mortality in the 15-39 years group not using HQ, four mortalities in the 40-59 years group not

using HQ, 38 mortalities in the 60 years and older group, of whom 33 did not use HQ and 5 did. In terms of comorbidity, while comorbid diseases were not found in 31 of the patients who died (31 deaths in 8.633 cases without comorbidities, 0.2%), a comorbid disease was seen in 12 of them (12 patients among 1084 cases with comorbid diseases, 0.7%). Details are given in (Table 2). In terms of pneumonia development, it was confirmed that pneumonia developed in 2.080 of the patients (10.8%). This number was found as 1286 (10.5%) in cases using HQ and as 794 (11.4%) in cases not using HQ. Pneumonia development in the age groups as per HQ use is given in (Table 3 and Figure 1).

Table 4 summarizes factors constituting risks for pneumonia development and the effect of HQ. Factors that might have an impact

Table 3: Pneumonia onset by age group, gender, comorbidity and HCQ use in COVID-19 patients monitorized with home care.

				Male			Female			Total		
				Pneumonia count	Pneumonia percent	Total N	Pneumonia count	Pneumonia percent	Total N	Pneumonia count	Pneumonia percent	Total N
Age Group	<15	Hydroxychloroquine Use	Absent	15	5.60%	269	15	5.10%	294	30	5.30%	563
			Present	24	5.20%	460	17	4.00%	424	41	4.60%	884
			Total	39	5.30%	729	32	4.50%	718	71	4.90%	1447
	15-39	Hydroxychloroquine Use	Absent	140	9.40%	1494	118	7.90%	1485	258	8.70%	2979
			Present	111	4.10%	2711	153	5.60%	2711	264	4.90%	5422
			Total	251	6.00%	4205	271	6.50%	4196	522	6.20%	8401
	40-59	Hydroxychloroquine Use	Absent	166	14.30%	1159	135	11.40%	1188	301	12.80%	2347
			Present	216	11.00%	1968	249	12.40%	2013	465	11.70%	3981
			Total	382	12.20%	3127	384	12.00%	3201	766	12.10%	6328
	60+	Hydroxychloroquine Use	Absent	98	18.70%	524	107	18.80%	570	205	18.70%	1094
			Present	269	27.60%	974	247	23.90%	1032	516	25.70%	2006
			Total	367	24.50%	1498	354	22.10%	1602	721	23.30%	3100
	All ages	Hydroxychloroquine Use	Absent	419	12.20%	3446	375	10.60%	3537	794	11.40%	6983
			Present	620	10.10%	6113	666	10.80%	6180	1286	10.50%	12293
			Total	1039	10.90%	9559	1041	10.70%	9717	2080	10.80%	19276
Comorbidity	Absent			880	9.90%	8854	797	9.20%	8633	1677	9.60%	17487
	Present			159	22.60%	705	244	22.50%	1084	403	22.50%	1789
All Patients				1039	10.90%	9559	1041	10.70%	9717	2080	10.80%	19276

Table 4: Factors associated with 14-day mortality in COVID-19 patients.

	p-value	Odds Ratio (OR)	Lower	Upper
Hydroxychloroquine effect[*]	<0.001	14.39	5.54	37.4
Age Group (ref: <40)[**]	<0.001			
40-59	0.113	5.88	0.66	52.72
60+	<0.001	116.5	15.87	856.11
Comorbidity presence	0.253	1.49	0.75	2.97
Gender (Male vs Female)	0.817	1.12	0.43	2.91
Hydroxychloroquine & Male Gender Interaction	0.36	2.44	0.36	16.46

[*]HCQ effect is described as the risk of mortality when HCQ is not used. I.e. the protective effect of HCQ use.
[**]Due to the very low number of events for mortality, a 3-tiered age grouping was used and no HCQ-age group interaction is introduced in the model.

on mortality and the effect of HQ are presented in (Table 5).

Discussion

There are a limited number of randomized-control and observational studies evaluating treatment with chloroquine and Hydroxychloroquine (HQ) in the COVID-19 disease [22-24]. In these studies, data on the efficacy of chloroquine and hydroxychloroquine are conflicting. These studies are criticized for not having undergone a peer-review, having small sample sizes and flawed methods [6]. Our study with a retrospective design can be considered suggestive with the presence of a relatively high number of patients. In our data, hydroxychloroquine use was continued for five days. When groups using and not using hydroxychloroquine were evaluated, the range of patient age was 0-101 years in the group using HQ and was 0-100 years in the group not using HQ. Mean and median age values of the patients using and not using HQ were found respectively as 40.5±18 and 39 years and 40.1±17.9 and 39 years. Considering that age has

a significant impact on the course of the disease, both groups were evaluated similar. In addition, female to male ratio in patients using and not using HQ was determined as 49.3/49.7 and 49.7/49.3 and was accepted similar.

When age groups, route of transmission, and onset of symptoms of our patients were evaluated, the numbers were given separately for 0-1 year, 2-11 years, 12-14 years, 15-18 years, 19-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, and 70 years and older. 12-14 years and 15-18 years age groups were formed due to the fact that these two age groups presented with more adult characteristics. However, in group comparisons, the groups were formed in terms of literature data and clinical course as 15 years and younger (n: 1447), 15-39 years (n: 8401), 40-59 years (n: 6328) and 60 years and older (n: 3100). Age groups and characteristics are given in (Table 1).

In a short report published in February 2020, chloroquine was used in more than a hundred patients, and it was stated that chloroquine

Table 5: Factors associated with risk of pneumonia onset in COVID-19 patients.

	p-value	Odds Ratio (OR)	95% CI for OR	
			Lower	Upper
Hydroxychloroquine effect*	0.097	1.128	0.979	1.3
Comorbidity presence	<0.001	1.762	1.547	2.007
Age Group (ref: <15)	<0.001			
15-39	0.02	1.359	1.05	1.758
40-59	<0.001	2.58	2.001	3.327
60+	<0.001	4.817	3.714	6.248
Gender (Male vs Female)	0.074	1.092	0.992	1.202
Hydroxychloroquine & Male Gender Interaction	0.021	1.253	1.035	1.518
Hydroxychloroquine & Age Interaction (ref:<15)	<0.001			
Hydroxychloroquine additional effect for 15-39	0.081	1.582	0.945	2.649
Hydroxychloroquine additional effect for 40-59	0.854	0.953	0.574	1.584
Hydroxychloroquine additional effect for 60+	0.041	0.584	0.348	0.979

*HCQ effect is described as the risk of pneumonia when HCQ is not used. I.e. the protective effect of HCQ use.

improved pulmonary findings in a shorter time compared to the control group, and virus clearance was ensured. However, no other detailed study was published regarding the study and control groups on this subject [22]. In a randomized control study performed during the early periods of the pandemic with 30 patients, the group receiving hydroxychloroquine (400mg/day, 5 days) and conventional treatment and the other group receiving only conventional treatment were compared, and a significant difference was not found in clinical results like fever and pulmonary imaging alterations and in 7 day viral clearance (87% *vs.* 95% p: >0.05) [23]. In another randomized control study comprising of 62 patients with mild symptoms (not receiving oxygen support despite findings in computerized tomography), earlier clinical improvement (cough: 2.0 days *vs.* 3.1 days; fever: 2c.2 days *vs.* 3.2 days) was shown in the group receiving standard treatment (antiviral agents, antibacterial agents, immunoglobulin, and corticosteroid) and hydroxychloroquine (400mg/day, 5 days) compared to the group receiving only the standard treatment [24]. A more significant improvement was confirmed in pneumonia findings radiologically (80% *vs.* 55%, p: <0.04) [24]. However, this study was published without peer review.

The recommendation of the Ministry of Health in Turkey was to use hydroxychloroquine the instant that the patient was suspected of COVID-19 possibility*. In this study, we retrospectively compared patients in whom hydroxychloroquine was started in the early period during sample collection and PCR positivity was confirmed thereafter and who did not show any clinical or radiological pulmonary findings and those that met the same conditions but did not receive treatment. Among the comparison criteria, we determined two main outcomes as targets: mortality and pneumonia development. (Table 2 and Table 3) respectively evaluates mortality and pneumonia development. Mortality in the group using hydroxychloroquine was seen in 5 patients in the 60 years and older age group; however, mortality in the group not using hydroxychloroquine was seen in one patient in the 15-39 years age group, four patients in the 40-59 years age group, and 38 patients in the 60 years and older age group (Table 2). In terms of first 14-day mortality, hydroxychloroquine use had a significant mortality-reducing effect in the 60 years and older age group. However,

despite the advantageous impression of the 40-59 years age group due to low mortality rate, the effect could not be achieved as much. Since it is known that sex and the presence of comorbid diseases generally affect mortality, the early start of hydroxychloroquine was shown to have a positive effect on survival when the effects of these factors were eliminated (Table 4). Early use of hydroxychloroquine in patients aged 15 years and older provides an advantage for survival close to 14.4 folds as odds ratio. When pneumonia development was evaluated (Table 5), it was seen that pneumonia developed more distinctively in young adults and young male adults. It was also established that its protective impact decreased in patients aged 60 years and older. The preventive-protective effect of early use of hydroxychloroquine against pneumonia development in patients aged 15 years and older is remarkable.

Conclusion

In conclusion, since this study confirmed that hydroxychloroquine used in outpatients presenting in the early period without any symptoms of pneumonia and in the evaluation of those having been in contact with a patient can ensure survival and prevent pneumonia development particularly in young adults, we believe that early use of hydroxychloroquine in mildly symptomatic patients results in a cost-effective and potent treatment. The study has some serious limitations including not having a prospective but a retrospective study design and no randomization. The effect of early use of hydroxychloroquine in well-defined, mildly-symptomatic patients will not be surprising considering the possible effect mechanism of hydroxychloroquine.

Ethical Approval

Approved by Ministry of Health Ankara Municipal Hospital Ethical Committee.

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