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Coronavirus Pandemic

Hydroxychloroquine shortened hospital stay and reduced intensive care unit admissions in hospitalized COVID-19 patients

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Abstract

Introduction: Effectiveness of hydroxychloroquine against SARS-CoV-2 has been highly controversial. In our research, we aimed to investigate the effects of hydroxychloroquine on disease outcomes in hospitalized patients with COVID-19.

Methodology: A total of 393 hospitalized patients with COVID-19 were retrospectively assigned to the standard of care therapy group (n = 180) or the standard of care plus hydroxychloroquine group (n = 213). The standard of care therapy comprised favipiravir, low molecular weight heparin, acetylsalicylic acid. Status of oxygenation at baseline and on the seventh day, laboratory tests at baseline and at discharge were recorded. Length of hospital stay, administration of anti-inflammatory treatment, admission to the intensive care unit and 28th day mortality were set as primary endpoints.

Results: There were no statistically significant differences between groups in terms of oxygen delivery route and mortality after seven days of treatment ($p = 0.592$). C-reactive protein levels of the standard of care plus hydroxychloroquine group were significantly lower than that of the standard of care group at discharge ($p = 0.034$). Patients in the standard of care plus hydroxychloroquine group had shorter hospital stay ($p = 0.007$). The standard of care plus hydroxychloroquine group was favored over standard of care group in terms of rate of intensive care unit admissions (21.7% *vs*. 10.8%; relative risk with 95% CI = 0.49 [0.31-0.80], $p = 0.003$).

Conclusions: Hydroxychloroquine in addition to standard of care was associated with less intensive care unit admissions, early discharge and greater C-reactive protein reduction. There was no difference in 28-day mortality.

Key words: COVID-19; hydroxychloroquine; intensive care unit; mortality; inpatient duration.

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Introduction

Coronavirus disease 2019 (COVID-19) has reached over 153.9 million positive cases and caused over 3.22 million confirmed deaths as of May 5, 2021 [1], globally. The majority of cases result in asymptomatic or mild illness. However, a significant number of patients suffer from a severe respiratory disease requiring hospitalization and progress to critical illness with hypoxemic respiratory failure [2]. There is still no proven curative agent for COVID-19, but a substantial number of therapeutics has been under investigation.

Hydroxychloroquine (HCQ) and chloroquine (CQ) are antimalarial drugs and have been available for more than a century, with well-established benefits, particularly in autoimmune diseases. Furthermore, HCQ has been demonstrated to have in vitro activity against *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) [3]. The effective inhibition of inflammatory cytokines such as interleukin-6 (IL-6), IL-1 and tumor necrosis factor alpha (TNFα) reduces tissue damage and endothelial inflammation, thereby has potential to prevent hyperinflammation [4].

There are numerous studies regarding the effectiveness of HCQ in COVID-19. In a randomized clinical trial, it was reported that those who received HCQ had significantly shorter clinical recovery time and higher recovery rate from pneumonia [5]. On the other hand, in a randomized, controlled, open-label study, a higher frequency of invasive mechanical ventilation or death was observed in HCQ group [6]. All in all, despite promising in vitro activity, the clinical effectiveness of HCQ against SARS-CoV-2 has been highly controversial.

In this study, we aimed to further evaluate possible benefits of HCQ when administered additionally to standard of care (SOC) therapy in COVID-19 by investigating rates of intensive care unit (ICU) admissions, anti-inflammatory treatment administrations, length of hospital stay and 28-day mortality.

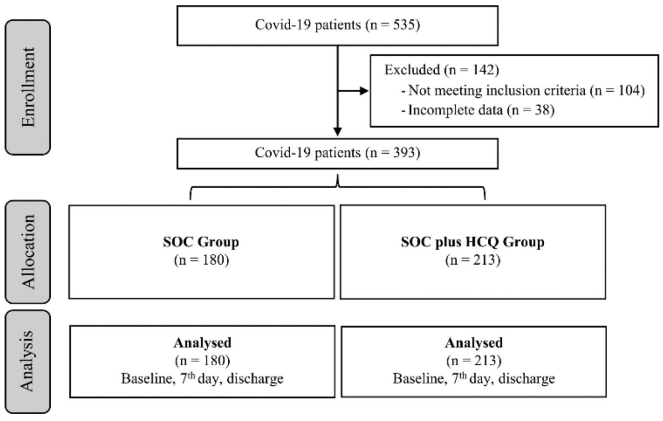
Methodology

In this retrospective, cohort study, adult cases who were admitted to Ankara City Hospital, internal medicine inpatient clinic with a diagnosis of COVID-19 between April 1 and December 31, 2020 were evaluated. COVID-19 diagnosis was confirmed in presence of a positive SARS-CoV-2 real-time reverse transcription polymerase chain reaction (RT-PCR) test from nasopharyngeal swab.

Data regarding patient demographics, disease course and administered medications were collected from hospital database using a standardized case-report form. All data was saved by the same physicians (HÇ and MA). Patient demographics, comorbid diseases, vital signs and symptoms of COVID-19 on admission, status of oxygenation at baseline and on the seventh day, laboratory parameters at baseline and at discharge were recorded. Length of hospital stay, administration of anti-inflammatory treatment, admission to the ICU and 28th day mortality were set as primary endpoints. Age under 18 years, pregnancy, lactation, immediate need for invasive mechanical ventilation on admission and vasopressor need on admission to maintain median arterial pressure over 65 mmHg were set as exclusion criteria.

SOC comprised favipiravir, low molecular weight heparin and acetylsalicylic acid. Patients who additionally received HCQ were grouped as SOC plus HCQ group. All treatments have been initiated on the first day of hospitalization. Demographic, laboratory, clinical data and endpoints were compared between groups. The general approach in treatment of COVID-19 in our clinic was determined by Turkish Health Ministry guidelines [7]. Accordingly, HCQ was generally administered with a dose of 400 mg/day without loading for five days (continued for 10 days in severe cases) and avoided in patients with a history of allergy to HCQ, retinopathy, cirrhosis, glucose-6-phosphate dehydrogenase (G6PD) deficiency, in patients with ventricular arrhythmia and elongated corrected QT interval (> 500 msec) in electrocardiography on admission and in patients who rejected HCQ. HCQ is added to the SOC group if there is no contraindications or patient disclaimer.

Figure 1. Flow chart of the study.



HCQ: hydroxychloroquine; SOC: standard of care.

Statistical analysis

Statistical analyses were made using Statistical Package for the Social Sciences version 22 (SPSS Inc., Chicago, IL, USA). Normality of variables were investigated by visual (histogram and probability graphics) and analytical methods (Kolmogorov-Smirnov test). Descriptive statistics were presented either with median and interquartile range (IQR) or mean ± standard deviation, according to normality. Categorical variables were presented with number and percentages. The Mann-Whitney-U test or the Student-t test was used for comparison of continuous variables according to normality. For the evaluation of categorical variables, the Pearson's Chi-Squared test and Fisher's final test were used. Relative risk (RR) values and their 95% CI were calculated through crosstabs. p values < 0.05 were considered statistically significant.

All procedures in this study were approved by Ankara City Hospital Ethics Committee and were therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments (IRB no. E2-20-94).

Results

Three hundred and ninety-three patients (183 females, 210 male) were included in the study. The patients' flow diagram is presented in Figure 1. A total of 180 patients received SOC therapy and 213 patients received SOC plus HCQ. There were no significant differences between the groups at baseline except the presence of fever (p = 0.032). Baseline demographic and clinical characteristics of the patients were presented in Table 1.

Table 1. Demographic and clinical characteristics of the patients at baseline.

Characteristics	SOC (n = 180), n (%)	SOC plus HCQ (n = 213), n (%)	*p* value
Male sex	97 (53.9)	113 (53.1)	0.868
Age (years), mean (SD)	63.9 (15.1)	62.7 (14.3)	0.46
Cough	93 (51.7)	103 (48.4)	0.513
Fever	54 (30)	86 (40.4)	0.032*
Dyspnea	88 (48.9)	120 (56.3)	0.14
Headache	15 (8.3)	23 (10.8)	0.41
Back Pain	9 (5.0)	6 (2.8)	0.26
Arthralgia	9 (5.0)	21 (9.9)	0.071
Myalgia	86 (47.8)	106 (49.8)	0.695
Nausea and vomiting	39 (21.7)	54 (25.4)	0.392
Anosmia	4 (2.2)	13 (6.1)	0.06
Ageusia	17 (9.4)	29 (13.6)	0.20
Hypertension	106 (58.9)	105 (49.3)	0.068
Diabetes	63 (35)	58 (27.2)	0.096
Asthma	12 (6.7)	22 (10.3)	0.198
COPD	15 (8.3)	11 (5.2)	0.208
CHD	60 (33.2)	62 (29.1)	0.367
Renal disease	36 (20.1)	30 (16.8)	0.112

SOC: Standard of care; HCQ: Hydroxychloroquine; CHD: Coronary heart disease; COPD: Chronic obstructive pulmonary disease; * $p < 0.05$.

Table 2. Comparison of type of oxygen delivery and death between groups at baseline and on 7th day of treatment.

	SOC (n = 180)	SOC plus HCQ (n = 213)	*p* value	SOC (n = 180)	SOC plus HCQ (n = 213)	*p* value
	Baseline			7th day of treatment		
Without oxygen supplement, n (%)	70 (38.9)	79 (37.1)	0.342	99 (55)	132 (62)	0.592
Nasal cannula or facemask, n (%)	108 (60)	124 (58.2)		65 (36.1)	62 (29.1)	
High flow nasal cannula, n (%)	2 (1.1)	8 (3.8)		5 (2.8)	7 (3.3)	
NIMV, n (%)	0 (0)	1 (0.5)		2 (1.1)	1 (0.5)	
Invasive mechanical ventilation, n (%)	0 (0)	1 (0.5)		8 (4.4)	8 (3.8)	
Death, n (%)	0 (0)	0 (0)		1 (0.6)	3 (1.4)	

SOC: Standard of care; HCQ: Hydroxychloroquine; NIMV: Non-invasive mechanical ventilation.

Table 3. Comparison of the laboratory parameters between groups at baseline and on discharge.

	SOC (n = 180)	SOC plus HCQ (n = 213)	*p* value	SOC (n = 180)	SOC plus HCQ (n = 213)	*p* value
	Baseline			Discharge		
Creatinine (mg/dL)	1.0 (0.71)	0.96 (0.4)	0.293	0.94 (0.6)	0.94(0.47)	0.740
AST (U/L)	32 (28)	37 (30)	0.043*	29 (23.7)	31 (25)	0.315
ALT (U/L)	25 (28)	31 (28)	0.027*	37.5 (45)	41.5(37.5)	0.086
LDH (U/L)	301 (180)	310 (154)	0.594	290 (153)	278 (132)	0.449
CRP (mg/L)	59 (111)	66 (103)	0.603	10 (24.8)	8 (15)	0.034*
ESR (mm/h)	41.5(30.5)	38 (36.5)	0.523	27 (35.5)	27.5(31.7)	0.996
Ferritin concentration (µg/L)	249 (564)	295 (519)	0.783	295 (572)	296 (492)	0.532
WBC (per mm^3)	5.7 (3.3)	6.3 (3.7)	0.078	7.7 (5.1)	8.1 (5.03)	0.389
Lymphocyte (per mm^3)	0.96(0.65)	1.05 (0.7)	0.071	1.25(1.01)	1.35 (1.1)	0.603
Albumin (g/L)	40 (5.92)	39.1 (6)	0.047*	35.1 (8.2)	35.8 (7.6)	0.082
CK (U/L)	92 (114)	89 (125)	0.812	34 (37)	37 (37.2)	0.646
D-Dimer (mg/L)	0.83(1.32)	0.89 (1.4)	0.976	0.66 (1.3)	0.73 (0.7)	0.631
Fibrinogen concentration (g/L)	4.6 (1.8)	4.7 (2.2)	0.213	3.6 (1.6)	3.6 (1.3)	0.553

SOC: Standard of care; HCQ: Hydroxychloroquine; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: White blood cell count; AST: Serum aspartate aminotransferase; ALT; Serum alanine aminotransferase; LDH: Lactate dehydrogenase; CK: Creatine kinase; g/L: gram/liter; mg/L: milligram/liter; mm: millimeter; U/L: units/liter; µg/L: micrograms/liter; mm/h: millimeters per hour. All laboratory parameters have been calculated as median (interquartile range). * $p < 0.05$.

Table 4. Demographic and clinical characteristics of the death patients at baseline.

Characteristics	SOC (n = 20), n (%)	SOC plus HCQ (n = 17), n (%)	*p* value
Male sex	14 (70)	10 (58.8)	0.478
Age (years), mean (SD)	73.5 (15.6)	75.1 (10.5)	0.892
Cough	10 (50)	11 (64.7)	0.368
Fever	10 (50)	7 (41.2)	0.591
Dyspnea	12 (60)	16 (94.1)	0.023*
Myalgia	4 (20)	5 (29.4)	0.506
Nausea and vomiting	5 (25)	4 (23.5)	1
Anosmia	0 (0)	1 (5.9)	0.459
Ageusia	2 (10)	3 (17.6)	0.498
Hypertension	16 (80)	11 (64.7)	0.297
Diabetes	6 (30)	9 (52.9)	0.157
Asthma	1 (5)	3 (17.6)	0.217
COPD	5 (25)	2 (11.8)	0.306
CHD	13 (65)	10 (58.8)	0.699
Renal disease	9 (45)	4 (23.5)	0.173

SOC: Standard of care; HCQ: Hydroxychloroquine; CHD: Coronary heart disease; COPD: Chronic obstructive pulmonary disease. * $p < 0.05$.

The status of oxygenation and rates of mortality of the groups at baseline and on the 7th day of treatment were given in Table 2. No significant differences between groups regarding type of oxygenation and rate of mortality at baseline and on 7th day of treatment (p = 0.342, p = 0.592, respectively) were observed.

There were no significant differences between the groups regarding laboratory parameters at baseline except for transaminases and albumin (AST, ALT, albumin; p = 0.043, p = 0.027, p = 0.047, respectively). C-reactive protein (CRP) levels of the SOC plus HCQ group were significantly lower than that of the SOC group at discharge (p = 0.034). Comparison of the laboratory parameters between the groups at baseline and on discharge were presented in Table 3.

Demographic and clinical characteristics of SOC and SOC plus HCQ recipients with mortality were given in Table 4. There was no significant difference in age and comorbidities. Dyspnea on admission was significantly more frequent in patients who received SOC plus HCQ treatment compared to the SOC group in deceased patients (16 [94.1] *vs*. 12 [60], p = 0.023).

Primary endpoints are presented in Table 5. Death at 28 days occurred in 20 of 180 patients (11.1%) in the SOC group and in 17 of 213 patients (8%) in the SOC plus HCQ group without significant difference between groups (relative risk with 95% CI = 0.71 [0.38-1.32], p = 0.29). Patients in the SOC plus HCQ group had a shorter hospital stay than the SOC group: median (IQR), 10 (7) days *vs*. 12 (1.5) days, p = 0.007. SOC plus HCQ group was favored over SOC for ICU admission (21.7% days *vs*. 10.8%; relative risk with 95% CI = 0.49 [0.31-0.80], p = 0.003).

Discussion

Our results demonstrated SOC with HCQ is associated with less intensive care unit admissions, early discharge and greater CRP reduction compared to the SOC group. There was no difference in 28-day mortality.

To date, different and contradictious clinical results have been reported in randomized, controlled studies evaluating HCQ for COVID-19 treatment. In a randomized, controlled, open-label study conducted by the RECOVERY group, 1,561 patients were randomized to receive HCQ and 3,155 patients to usual care. In the hydroxychloroquine group, patients received HCQ with a loading dose (total dose, 800 mg) at baseline and, which was followed by 400 mg daily for the next nine days or until discharge. Death within 28 days occurred in 421 patients (27.0%) in the HCQ group and in 790 (25.0%) in the usual-care group. Rate of invasive mechanical ventilation or death during follow-up was increased in HCQ group (30.7% *vs*. 26.9%). As a result, among patients hospitalized with COVID-19, additional HCQ did not seem to be beneficial [6]. In another multicenter, randomized controlled trial from Egypt, 194 patients with a

Table 5. Evaluation of the patients' outcome between the groups.

Outcome	SOC (n = 180)	SOC plus HCQ (n = 213)	*p* value
Inpatient duration (days), median (IQR)	12 (10.5)	10 (7)	0.007*
Need to anti-inflammatory treatment, n (%)	116 (64.4)	141 (66.2)	0.716
Intensive care unit admission, n (%)	39 (21.7)	23 (10.8)	0.003*
28-day mortality, n (%)	20 (11.1)	17 (8.0)	0.29

* $p < 0.05$.

diagnosis of COVID-19 were equally randomized into two treatment arms; 97 receiving HCQ plus standard care and 97 receiving standard care alone. HCQ was initiated 800 mg on first day followed by 200 mg twice daily for 15 days. The primary endpoints were recovery within 28 days, the need for mechanical ventilation or death. Overall mortality did not differ between the two groups, as six patients (6.2%) died in the HCQ group and 5 (5.2%) in the control group. It was demonstrated that HCQ treatment was not significantly associated with reduced mortality in COVID-19 patients [8]. In a large-scale observational study of 1,376 COVID-19 patients in New York, 58.9% of them received 600 mg of HCQ twice on day 1 and then 400 mg per day for an average of 5 days. However, administration of HCQ was not associated with composite intubation or death endpoint (hazard ratio = 1.04; 95% CI = 0.82, 1.32) [9]. On the contrary, in a large-scale observational study conducted on 2,541 COVID-19 patients, it was demonstrated that HCQ administration resulted in a 66% reduction in in-hospital mortality [10]**.** Furthermore, in a retrospective observational multicenter study of 8910 hospitalized patients with COVID-19, in which 4542 received HCQ as monotherapy (a total of 2,400 mg over 5 days) in addition to supportive care while 3533 received supportive care alone, a reduced mortality rate was observed in HCQ group (17.7 % *vs*. 27.1 %). Compared to supportive care alone, low-dose HCQ monotherapy was independently associated with lower mortality in hospitalized patients with COVID-19 [11]. Our results did not demonstrate a reduction in 28-day mortality with additional HCQ.

In a single-center, retrospective, observational study from our country, rates of admission to ICU in mild/moderate COVID-19 patients treated with HCQ, favipiravir, and HCQ plus favipiravir were investigated. A total of 824 patients were evaluated, with HCQ, favipiravir and HCQ plus favipiravir groups consisting 604, 100 and 120 patients, respectively. HCQ group received 800 mg HCQ on day 1 and 400 mg on days 2–5, favipiravir group received 3200 mg favipiravir on day 1 and 1200 mg on days 2–5, favipiravir plus HCQ group received 800 mg HCQ plus 3200 mg favipiravir on day and 400 mg HCQ plus 1200 mg favipiravir on days 2-5. Results of this study revealed that HCQ with or without favipiravir therapy was associated with a reduced risk of ICU admission in adult patients with mild to moderate COVID-19 compared to favipiravir alone [12]**.** Similarly, our study demonstrated that standard of care plus HCQ treatment was associated with less ICU admission compared to standard of care alone.

In SOLIDARITY trial, in 11,330 patients from 405 centers and 30 countries, effects of different therapeutic agents including remdesivir (2,750 patients), hydroxychloroquine (954 patients), lopinavir without interferon (1,411 patients), lopinavir plus interferon (651 patients), interferon (1,412 patients) and no trial drugs (4,088 patients) were evaluated. The HCQ regimen was two 800 mg administrations with six-hour interval followed by 800 mg for 10 days. None of the agents were reported to reduce mortality and hospital stay in general or in any subgroup [13]. In our study additional HCQ administration was associated with shorter hospital stay.

HCQ and CQ are used in the treatment of many rheumatic diseases such as rheumatoid arthritis and lupus erythematosus besides malaria due to anti-inflammatory and immunomodulatory effects. Typical innate immune response against SARS-CoV-2 is associated with suppressed type I interferon. Toll-like receptor (TLR) 7 plays a substantial role in recognition of SARS-CoV-2 genome and initiation of the innate immune response [14]. By increasing endosomal pH, HCQ decreases the affinity of TLR 7 and TLR 9 for viral RNA, possibly hampering proinflammatory cytokine release including type I interferon, IL-6, and IL-12 [15]. With the inhibition of endosome acidification, HCQ also interferes antigen processing and presentation, which alters both T cell and B cell responses, therefore affecting both adaptive and innate immunity. Treatment with CQ/HCQ reduces the number of proliferating T cells and limits differentiation towards T helper (Th) 1 and Th17 [16]. Reduced antigen presentation further limits IL-6 and TNFα expression by decreased induction of CD4 Th cells [17]**.** Through these immunomodulatory mechanisms HCQ has potential to prevent progression to severe disease with excessive inflammatory responses by limiting cytokine release. In addition, post-COVID-19 syndrome is an emerging problem in disease survivors, since the infection has also been linked with development of a prolonged inflammatory state and related clinical manifestations. In a case series which evaluated this so-called "post-COVID inflammation syndrome", non-specific inflammation and post-viral arthritis were defined in three cases and vasculitis causing central retinal artery occlusion in another case. The short-term administration of nonsteroidal anti-inflammatory drugs and HCQ has been found to be beneficial for alleviating symptoms [18]. In our study, significantly lower CRP levels were

observed at discharge in HCQ group suggesting a better control of inflammation and a potential to reduce the risk of developing post-COVID syndrome can be speculated.

Different treatment doses were used in randomized studies of HCQ and CQ. In a randomized double-blind pre-clinical study conducted in Brazil, participants received high dose CQ (600mg CQ twice daily for 10 days, or 12 grams total) or low dose CQ (450mg for 5 days, twice daily on the first day only or total dose 2.7 grams).. Additionally, all patients were treated with ceftriaxone and azithromycin. QT interval elongation was observed 25% more in high dose CQ arm. Mortality rate was also higher in the high dose group. The study was halted due to safety concerns and no clear benefit with higher CQ doses [19]**.** Excessive doses of CQ were possibly associated with higher mortality. General approach in our inpatient clinic for COVID-19 treatment comprises administration of HCQ with a daily dose of 400 mg for five days without loading, which may be continued for ten days according in severe cases, with a far less cumulative antimalarial dose.

HCQ and CQ are generally considered as safe drugs. The most common side effects include gastrointestinal symptoms, itching, and dermatological changes [20]. COVID-19 has been reported to affect heart tissue, and besides, some safety concerns have arisen regarding life-threatening side effects such as cardiac arrhythmias during the pandemic, especially when HCQ is combined with certain other medications. [19]. The RECOVERY and SOLIDARITY trials reported that HCQ at a study dose of 9,200-9,600 mg for 10 days had no benefit in hospitalized patients with COVID-19 [6,13]. Inappropriate and excessive dosing regimens and multidrug combinations which have been used during the pandemic are likely to be responsible for these adverse events. Chronic administration of HCQ for rheumatological disorders has not been associated with major safety signals after decades of use. No association was found between QTc length and hydroxychloroquine use in a total of 681 SLE and RA patients without clinical cardiovascular disease (CVD) [21]. In addition, in our study, no difference was found in terms of cardiac disease history in the comparison of patients who died under SOC and SOC plus HCQ groups [5 (25) *vs*. 2 (11.8), $p = 0.306$].

Our trial has several limitations. In addition to the retrospective nature of the study and lack of randomization, most prominent limitation seems to be the absence of a comprehensive evaluation of adverse events, particularly cardiac side effects. However, no differences were shown between the groups in terms of overall mortality and changes in liver kidney function. Since the clinical course of COVID-19 is highly variable, the efficacy of HCQ should be evaluated in multi-center studies, alone or in combination with other drugs, and in larger populations at different doses and durations.

In conclusion, our study suggests less admission to the ICU, shorter hospital stay and lower CRP levels at discharge with HCQ when administered in addition to the standard of care in COVID-19 patients. To date, no curative agent or treatment protocol has been defined for COVID-19. Increased demand for hospitalization and ICU admission has become one of the most crucial aspects of the pandemic, therefore shortening the hospital stay and decreasing ICU admission rate by HCQ can make a significant contribution to overall patient care and management. Place of HCQ in management of post-COVID inflammatory syndromes may be considered as a research topic for future trials since better control of inflammation was obtained with HCQ.

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