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Original Article

Use of Hydroxychloroquine in Patients with COVID-19: A Retrospective Observational Study

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Abstract

OBJECTIVE: There is no consensus on a certain drug therapy for COVID-19 infection. Growing reports argue about the potential benefits of hydroxychloroquine (HCQ) in reducing morbidity and mortality in patients hospitalized with COVID-19, but with inconsistent results.

This study aimed to assess the potential benefits of HCQ on viral conversion, reducing the need for ICU or mechanical ventilation, and its impact on mortality.

MATERIAL AND METHODS: This retrospective observational study was conducted enrolling confirmed SARS-CoV2 patients. They were subjected to plain CXR (HRCT of chest if needed), routine laboratory tests for COVID-19 (including CBC, CRP, LDH, D-Dimer, ferritin, and blood sugar), ECG, and blood gases. They were allocated to either HCQ or non-HCQ groups. Both groups were followed-up for symptoms resolution, need for ICU admission, non-invasive or invasive ventilation, duration till conversion, and mortality.

RESULTS: A total of 202 patients with moderate COVID-19 were enrolled with a mean age of 55.05±10.15, out of whom 80% were male patients. The most common presenting symptom was fever (87.38% in the control group versus 92% in the HCQ group), followed by cough (82.52% versus 89.9%). In total, 24.27% of patients in the control group versus 28.3% in the HCQ group deteriorated and necessitated ICU admission (p=0.52), 13.6% of the control group versus 19.2% in the HCQ group required mechanical ventilation (p=0.28), and 69.9% of the control group versus 68.9% in the HCQ group converted negative on day 7 (p=0.85). No significant mortality difference between both groups was observed (4.9% versus 6.1%, p=0.47).

CONCLUSION: This work did not support any benefits of using HCQ in patients with COVID-19, neither in reducing the need for ICU, mechanical ventilation, nor mortality.

KEYWORDS: Hydroxychloroquine, COVID-19, SARS-CoV2, ICU, mortality

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INTRODUCTION

Corona viruses are important human and animal pathogens. Towards the end of 2019, a novel corona virus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in a global pandemic. The disease is termed as COVID-19, which stands for the corona virus disease 2019 [1].

There is no consensus on a certain drug therapy for COVID-19 infection as yet. A lot of drugs are under trial or are empirically included in treatment protocols for COVID-19. Drug re-purposing is the most widely used method for rapid response in the face of this epidemic. Trials to invent *de novo* medicines may not be the perfect rationale, while the death and infection toll is on the rise by the hour. Hydroxychloroquine (HCQ) is an antimalarial and antirheumatic immunomodulating agent that has been suggested as an effective treatment for COVID-19 because of its anti-inflammatory and antiviral effects [2-5].

Growing reports argue about the potential benefits of HCQ in reducing morbidity and mortality in patients hospitalized with COVID-19, but with inconsistent results [6]. So, the current work was conducted to test the potential benefits of HCQ on viral conversion, reducing the need for ICU, mechanical ventilation, and its impact on mortality.

MATERIAL AND METHODS

This is a retrospective observational study. It was carried out at the Saudi National Hospital, Mecca, KSA, after obtaining the approval of the administrative manager and the hospital ethical committee. Patients with full files with document-

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ed outcome were enrolled in this study in the period from March 21st to June 8th, 2020. Patients (aged ≥18 years) included were those who were admitted due to clinical and radiological picture suggestive of COVID-19, with documented qualitative RT-PCR swab positive for SARS-CoV2 virus. A total of 202 patients were selected, out of whom 162 were men and 40 were women. All of them were graded as moderate COVID-19 cases, with regard to disease severity. The severity of COVID-19 was graded as follows: (1) mild—mild clinical symptoms, no pneumonia on lung CT; (2) moderate—fever, cough and lung CT with pneumonia without need for ICU; (3) severe—respiratory distress (respiratory rate > 30 min-1, oxygen saturation (O2Sat) ≤ 93% at rest, and/or ratio of arterial oxygen partial pressure to fractional inspired oxygen ≤300 mmHg (PaO2/FIO2); and (4) critical—aforementioned criteria of respiratory failure receiving mechanical ventilation, shock, and/or organ failure other than lung, and/or intensive care unit (ICU) hospitalization [7, 8].

Patients with undetermined RT-PCR results, no follow-up PCR, or with severe disease were excluded. Patients with a history of arrhythmias or those who were receiving treatment for the same were excluded from the HCQ group.

Patients were classified into two groups according to treatment administered:

- Hydroxychloroquine (HCQ) group: This group included 99 patients (with a mean age of (55.5±9.8 years), out of whom 78 were men (78.79%), with 27 (27.27%) smokers. They received HCQ oral at dose of 400 mg twice a day on the 1st day, followed by 200 mg twice a day for the next 5 days (14 tablets total). Besides, they received the usual standard of care management.
- Non-HCQ group: This group included 103 patients (with a mean age of 54.6±10.5 years), out of whom 84 were men (81.55%), with 33 (32.04%) smokers. They received only standard of care management in the form of broad-spectrum antibiotics based upon the local antibiogram—azithromycin 500 mg daily for 5–6 days, paracetamol oral or intravenous (IV) every 6–8 hours as needed, along with O_2 therapy, corticosteroids, and anticoagulants in moderate cases.

The following was done on first day of admission:

- Patient history was collected, stressing on smoking and co-morbidities, clinical examination, plain CXR (non-contrast HRCT of chest if needed), oro- and nasopharyngeal swabs for SARS-CoV2 RT-PCR, and routine laboratory tests for COVID-19 patients (CBC, CRP, LDH, D-Dimer, LFT, RFT, blood sugars, and electrolytes), ECG, ABGs, and other tests according to patient co-morbidities.

MAIN POINTS

- HCQ did not reduce time to conversion.
- HCQ did not reduce the need of ICU admission.
- HCQ did not significantly affect mortality.

- Then, after confirmation by RT-PCR, they were allocated to either the HCQ or non-HCQ groups.

Both groups were followed up for:

- Symptoms resolution and onset of new symptoms
- SpO_2 checked frequently every day or ABGs as needed
- Follow-up of the admission investigations every 2 days or in case of deterioration
- Daily ECG for HCQ group or as needed
- Assessment of need for O_2 therapy
- Need for ICU admission
- Need for non-invasive ventilation
- Need for invasive mechanical ventilation
- Duration till conversion (swab repeated every 72 hours till two negative swabs 24 hours apart)
- Length of hospital stay was recorded
- Survival and discharge, or death

Power analysis was performed using the Chi-square test for independent samples on the frequency of patients virologically cured, as it was the primary aim of our study. According to Gautret et al. [9] (at 6 days of follow-up), the virologically cured constituted a total of 12.5 % of control group versus 57.1% of HCQ group. Taking a power of 0.8 and alpha error of 0.05, a minimum sample size of 17 patients was calculated for each group. A total of 202 eligible patients were retrieved and included in the study as inflation of sample size has an advantage of increased power of study and minimized alpha error (MedCalc 13 for windows, MedCalc Software bvba, Ostend, Belgium).

Statistical Analysis

The statistical analysis was done using Minitab 17.1.0.0 for windows (Minitab Inc., 2013, Pennsylvania, USA). Data normality was examined using Shapiro Wilk test, continuous data were represented as mean and standard deviations (SD), and categorical data as number and percentage (%). Comparison between the two means was done using an independent t-test, while the Chi-square test compared the frequency between the two groups or more. All tests were two sided, and p value was considered significant if $p < 0.05$.

RESULTS

A total of 202 patients with mild to moderate COVID-19 were enrolled in this study. The mean age of these patients was 55.05±10.15, and 80% were men. They were randomized to either HCQ group or the standard-of-care group (control group). Both groups were matched with regard to age, gender, smoking status, and co-morbid profile (Table 1). Clinico-laboratory parameters are shown in Table 2. The most common presenting symptom was fever (87.38% in the control group versus 92% in the HCQ group), followed by cough (82.52% versus 89.9%) and dyspnea (66.9% versus 71.7%).

With regard to the radiological presentation of the studied population (Table 3), in the control group, 53.4% of patients presented with abnormal x-ray infiltrates (42.7% presented with bilateral infiltrates, while 10.7% presented with unilateral abnormalities).In the HCQ group, 59.6% of patients presented with abnormal x-ray infiltrates (50.5% presented

with bilateral infiltrates, while 9.1% presented with unilateral abnormalities).In computed tomographic study, the most common presenting radiological pattern was ground glass opacities (75.7% in the control group versus 84.9% in the HCQ group).

HCQ as a therapeutic option for patients with COVID-19 did not affect either the clinical outcome or mortality, as shown in Table 4. In total, 24.27% of patients in the control group versus 28.3% in the HCQ group deteriorated and necessitated ICU admission (p = 0.52), 13.6% in the control group versus 19.2% in the HCQ group required mechanical ventilation (p=0.28), and 69.9% in the control group versus 68.9% in HCQ group converted negative at day 7, without any statistical difference (p=0.85). The duration from positive PCR result till conversion to negative were 9.48±1.09 days in

Table 1. General characteristics of the studied groups

	Control group (n=103)		HCQ group (n=99)		
Factors	**Mean/n**	**SD/%**	**Mean/n**	**SD/%**	**p**
Age	54.6	10.5	55.5	9.8	0.53*
Sex (male)	84	81.55	78	78.79	0.62‡
Smoking status (Yes)	33	32.04	27	27.27	0.46‡
Co-morbidity					
DM	21	20.4	27	27.3	0.25‡
Hypertension	23	22.3	28	28.3	0.33‡
Ischemic heart Diseases	9	8.74	6	6.06	0.47‡
Bronchial asthma	12	11.7	10	10.1	0.72‡
COPD	3	2.91	2	2.02	0.68‡

SD: standard deviation, n: number, continuous data represented as mean and SD, and categorical data represented as number and percentage (%)
*Independent samples Student's t-test; ‡Chi-square test; p<0.05 is significant

Table 2. Clinico-laboratory presentation

	Control group (n=103)		HCQ group (n=99)		
Factors	**Mean/n**	**SD/%**	**Mean/n**	**SD/%**	**p**
Fever	90	87.38	92	92.9	0.19‡
Cough	85	82.52	89	89.9	0.13‡
Expectoration	10	9.71	6	6.06	0.34‡
Dyspnea	69	66.9	71	71.7	0.47‡
Myalgia	63	61.2	67	67.7	0.33‡
Sore throat	39	37.86	29	29.29	0.20‡
Hemoptysis	6	5.8	8	8.08	0.53‡
Diarrhea	55	53.4	65	65.7	0.08‡
Loss of smell	29	28.16	37	37.37	0.16‡
Anorexia	27	26.21	22	22.22	0.51‡
TLC	5.91	1.95	6.29	2.48	0.23*
HB	14.82	2.13	15.42	1.46	0.022*
Platelet	196.9	59.3	201.3	67.5	0.62*
Lymphocytic %	20.1	7.92	19.39	7.04	0.5*
CRP	34.5	19.5	39.8	18.9	0.05*
Ferritin	347	199	355	168	0.76*
LDH	353	160	362	224	0.74*
ALT	46.9	22.6	52.6	31.3	0.14*
ALT	44.2	12.3	46.4	17.4	0.29*
Creatinine	0.96	0.151	0.94	0.223	0.45*
K	3.5	0.422	3.6	0.498	0.12*
Na	131.71	4.35	131.06	4.81	0.314*

SD: standard deviation, n: number, continuous data represented as mean and SD, and categorical data represented as number and percentage (%)
*Independent samples Student's t-test; ‡Chi-square test; p<0.05 is significant

Table 3. Radiological pattern

Factors	Control group (n=103)		HCQ group (n=99)		p
	Mean/n	SD/%	Mean/n	SD/%	
X-ray abnormality (Yes)	55	53.4	59	59.6	0.37‡
Side of lesion (X-ray)					
Unilateral	11	10.7	9	9.1	0.71‡
Bilateral	44	42.7	50	50.5	0.27‡
Pattern (CT)					
Reticular shadows	13	12.62	9	9.1	0.23‡
GGO	78	75.7	84	84.9	0.1‡
Nodules	2	1.94	6	6.1	0.13‡

SD: standard deviation, n: number, categorical data represented as number and percentage (%). ‡Chi-square test; p<0.05 is significant

Table 4. Outcome of studied groups

Factors	Control group (n=103)		HCQ group (n=99)		p
	Mean/n	SD/%	Mean/n	SD/%	
Need for ICU	25	24.27	28	28.3	0.52‡
Need for MV	14	13.6	19	19.2	0.28‡
% of conversion at day 7	72	69.9	68	68.69	0.85‡
Duration till conversion (days)	9.49	1.09	9.86	2.56	0.18*
LOS in hospital (days)	8.99	2.46	9.43	2.62	0.22*
Death	5	4.9	6	6.1	0.71‡

SD: standard deviation, n: number, continuous data represented as mean and SD, and categorical data represented as number and percentage (%). MV: mechanical ventilation; LOS: length of stay
*Independent samples Student's t-test; ‡Chi-square test; p<0.05 is significant

the control group versus 9.86±2.56 days in the HCQ group (p=0.07).The total hospital length of stay was 8.99±2.46 days in the control group versus 9.43±2.62 days in the HCQ group (p=0.22). With regard to the mortality rates in both groups, no significant statistical difference was found between both groups (4.9% versus 6.1%, p=0.47).

DISCUSSION

In this study, we found that hydroxychloroquine did not reduce the need for ICU admission and mechanical ventilation. Also, no significant difference was found between the HCQ and control groups with regard to the duration till swab conversion or hospital length of stay. Lastly, we found that there was no significant influence of using HCQ on the mortality rate.

HCQ is a potent immunomodulator, disease-modifying and rheumatic drug. It can increase the intracellular pH and inhibit lysosomal activity in antigen-presenting cells. *In vitro* studies highlighted its antiviral effects against SARS-CoV-2 with superiority over chloroquine with regard to higher potency and less toxicity [10-12].

The findings from an early study showing a benefit of HCQ in 26 patients who had been treated in French hospitals are questionable due to the small sample size, the absence of a randomized control group, and the exclusion of 6 patients from the analysis [6, 9].

A number of subsequent clinical trials have been conducted in China to test the efficacy and safety of chloroquine and HCQ in treatment of COVID-19-associated pneumonia, and according to the preliminary results on improving lung imaging, promoting a virus negative conversion, experts from government and regulatory authorities and organizers of clinical trials in a conference held on February 15,2020 agreed that chloroquine phosphate has potent activity against COVID-19 [13].

In uncontrolled non-comparative observational study conducted on 80 mild cases treated with a combination of HCQ and azithromycin, a rapid fall of nasopharyngeal viral load was noted with 83% negative on day 7 and 93% on day 8. In contrast, Tang and colleagues concluded that, HCQ did not significantly increase the probability of negative conversion than the standard of care [14, 15].

A randomized controlled trial was conducted in Shanghai, China on 30 adult patients with COVID-19 revealed that the HCQ group did not differ from the control group neither in number of patients testing negative on day 7 nor the duration of illness [16].

In one observational study conducted on a group of 1,438 patients in Metropolitan, New York, treatment with HCQ, either alone or combined with azithromycin, compared with neither treatment was not significantly associated with differences in mortality. In a retrospective report analyzing data

from 368 patients hospitalized with SARS-CoV-2, an association of increased overall mortality was identified in patients treated with HCQ. Moreover, the use of HCQ either alone or in combination with azithromycin did not reduce the risk of MV in hospitalized patients with COVID-19 [17, 18].

In conclusion, this study did not support any benefits of using HCQ in hospitalized patients with COVID-19, either in reducing the need for ICU admission, mechanical ventilation, or mortality.

Ethics Committee Approval: Ethics Committee approval for the study was obtained from the Hospital Ethical Committee Saudi National Hospital (SNH1352020).

Informed Consent: As it was a retrospective study, informed consent was not required.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.A., W.S.; Design- A.A., W.S.; Supervision - W.S.; Materials - W.S.; Data Collection and/or Processing - S.M.L.; Analysis and/or Interpretation - S.M.L., A.A., W.S.; Literature Review - A.A.; Writing - A.A., W.S.; Critical Review - S.M.L., A.A., W.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

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