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The effects of Hydroxychloroquine on COVID-19 in Tabuk, Saudi Arabia

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ABSTRACT

Background: Hydroxychloroquine (HCQ) has anti-inflammatory and immunomodulatory effects. Its use among patients with COVID-19 is a matter of controversy. Also, previous studies mostly assessed hospitalized patients who were more likely severely infected. Literature in the Kingdom of Saudi Arabia lack, thus, the current study investigated the role of HCQ in patients affected with COVID-19 visiting an outpatient specialized COVID-19 in Tabuk City, Saudi Arabia. *Subjects and Methods*: This is a case-control study conducted among 399 patients with COVID-19 at Tatamman Clinic, Tabuk City, Saudi Arabia during the period from August 2020 to December 2020. One hundred ninety-nine were given HCQ and those who refused the treatment were considered as controls). Demographic data, vital signs, and baseline symptoms including fever, sore throat, cough, loss of smell, difficulty in breathing, and other gastrointestinal symptoms were recorded. The patients were followed and for the reported symptoms. All the participants signed a written informed consent and the Statistical Package for Social Sciences (SPSS) was used for a comparison between intervention and control groups. *Results*: They were 399 patients with COVID-19 matched for age and sex. No significant differences between the intervention and control group regarding COVID-19 symptoms. *Conclusion*: Covid-19 symptomatology was no affected by HCQ treatment and its use in mild-moderate disease and chemoprophylaxis is not recommended.

Keywords: Hydroxychloroquine, COVID-19, symptoms, Saudi Arabia

1. BACKGROUND

COVID-19 epidemic is the worst worldwide pandemic, the number is rapidly rising with a lot of mortality and morbidity, in the Kingdom of Saudi Arabia, and more than two hundred were affected up to August 2020. An effective treatment is urgently needed

pending the availability of a vaccine to prevent the disease. Hydroxychloroquine was shown to be effective in reducing viral load among patients with Covid-19, and its effects were reinforced by azithromycin (Gautret et al., 2020) The drug acts through its immunomodulation, anti-inflammatory (inhibit interleukin-1, interferon-α, and tumor necrosis factor), and lysosomotropic action (Offerhaus et al., 2020). Studies conducted in France showed no effect of hydroxychloroquine in reducing the viral load (Molina et al., 2020). Other studies conducted in the US and Canada showed that hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection when used as post-exposure prophylaxis within 4 days after exposure (Boulware et al., 2020). A pilot study conducted in China showed a good prognosis among patients with moderate COVID-19 when HCQ was introduced (Chen et al., 2020). A randomized controlled trial published in China reported higher side effects among patients who received HCQ with no improvement of negative conversion probability (Tang et al., 2020). In addition, studies showed the effectiveness of interferon-β-1a in combination with hydroxychloroquine and lopinavir/ritonavir in the management of COVID-19, (Dastan et al., 2020). Further trials are still ongoing in Pakistan and other parts of the World. Importantly, the previous studies mostly investigated Hospital patients who are more likely severely infected. There is controversy regarding the effectiveness of HCQ among patients with Covid-19, the literature in Saudi Arabia is lacking. Given the above, we conducted this research to assess the effects of HCQ on COVID-19 in an outpatient-screening clinic in Tabuk City, Saudi Arabia.

2. SUBJECTS AND METHODS

Study design

This is a case-control study conducted among 399 patients with COVID-19 at Tatamman Clinic, Tabuk City, Saudi Arabia during the period from August 2020 to December 2020. All the patients who came with respiratory symptoms and confirmed with Covid-19 were approached. All adults who came with symptoms to confirm their COVID-19 status and who agreed to participate were included. Children, pregnant women, and those with diseases that contraindicate HCQ use were not included. The purpose of the research was clearly explained to the participants and they assured that the participation is voluntary and the data collected would be used confidentially and for this research only.

Sample size calculation

The Fiche formula (Charan et al., 2013) for case-control studies was used to calculate the sample size assuming that the prevalence of Covid-19 in Tabuk is unknown (50%) with 5% *CI,* the sample size will be 400 patients.

Intervention: The patients have prescribed hydroxychloroquine tabs and those who refused the treatment were considered control subjects. The participant was then followed for the baseline symptoms.

Data collection tool

Structured questionnaires are used to collect demographic data, chronic diseases including diabetes mellitus, hypertension, heart disease, renal disease, and bronchial asthma. Symptoms including fever, sore throat, cough, loss of smell, difficulty in breathing, and other gastrointestinal symptoms were reported, the vital signs were also measured. The status of hydroxychloroquine (compliance) was noted. All the participants were tested for COVID-19 (RT-PCR).

Ethical consideration

Informed consent: Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript. The study was approved by the Medical Ethics Committee of the Medical College, University of Tabuk. Ethical approval code is: READ 0113.

Data Analysis

The Statistical Package for Social Sciences (SPSS version 16, New York) was used for data analysis, the data were presented as a mean± SD or percentages unless otherwise specified with a P-value< 0.05 considered significant. The chi-square was used to compare the case and control.

3. RESULTS

They were 399 patients with Covid-19 (199 were started HCQ and 200 refused the treatment or the drug was contraindicated). The two groups were matched for sex (64.3% of patients were males vs. 56%, P-value, 0.252, 95% *CI,* 0.79-2.48) Nine (4.5%) of the interventional group were in the range 20-60 years compared to their counterparts (48.7%), while 94.5% versus 51.3% of controls

were in the range 60-65 years with no significant statistical difference, P-value, 0.995, 95% *CI*, 0.49-1.68. No significant difference was evident regarding comorbidities, 19% VS. 21.5% among the interventional group and controls respectively, P-value, 0.320, 95% *CI*, 0.76-2.35 (Table 1).

Table 1 Basic characters of the study group.

Character	HCQ	Controls	P-value	95% *CI*
Age 20-60 60-65	9 (4.5%) 190 (94.5%)	87 (48.7%) 102 (51.3%)	0.955	0.91(0.49-1.68)
Sex Males Females	128 (64.3%) 71 (35.7%)	112 (56.0%) 88 (44.0%)	0.252	1.40 (0.79-2.48)
Comorbidities Diabetes mellitus Hypertension Bronchial Asthma Renal disease	15 (7.5%) 12 (6.0%) 10 (5.0%) 1.0 (0.5%)	16 (8.0%) 13 (6.5%) 10 (5.0%) 4.0 (2.0%)	0.320	1.34 (0.76-2.35)

Compliance 80.9%

In the present study, vomiting was the commonest presentation (in 100%) followed by cough with no significant statistical difference between the intervention and control group (62.3% and 55.8%, P-value, 0.221), myalgia and headache were commoners among the HCQ group with significant statistical differences (56.3% vs. 45.2%, P-value, 0.035, and 54.3% vs. 34.2%, P-value, 0.000 respectively). Other symptoms were depicted in table 2.

Table 2 A comparison between patients and controls regarding COVID-19 symptomatology (At baseline)

Character	HCQ	Controls	P-value
Fever	101 (50.8%)	102 (51.3%)	1.00
Loss of smell and taste	30 (15.1%)	27 (13.6%)	0.671
Cough	124 (62.3%)	111 (55.8%)	0.221
Sore throat	74 (37.2%)	91 (45.7%)	0.103
Dyspnea	74 (37.2%)	56 (28.1%)	0.069
Headache	108 (54.3%)	68 (34.2%)	<0.001
Fatigue	10 (5.0%)	2 (1.0%)	0.036
Myalgia	112 (56.3%)	90 (45.2%)	0.035
Diarrhea	22 (11.1%)	26 (13.1%)	0.645
Vomiting	199 (100%)	199 (100%)	

During the disease course, all the symptoms improved among intervention and control groups except for the loss of smell, however, the control group showed a higher sore throat (9.5% vs. 3.5%, P-value, 0.024) and a lower headache compared to the intervention group (8.5% vs. 16.1%, P-value, 0.023) (Table 3).

Table 3 A comparisons between patients and controls regarding COVID-19 symptomatology (Three days after presentation)

Character	HCQ	Controls	P-value	95% *CI*
Fever	22 (11.1%)	24 (12.0%)	0.876	0.91(0.49-1.68)
Loss of smell and taste	32 (16.1%)	24 (12.0%)	0.252	1.40 (0.79-2.48)
Cough	37 (18.6%)	43 (21.5%)	0.532	0.83 (0.51-1.36)
Sore throat	7 (3.5%)	19 (9.5%)	0.024	0.34 (0.14-0.84)
Dyspnea	32 (16.1%)	25 (12.5%)	0.320	1.34 (0.76-2.35)
Headache	32 (16.1%)	17 (8.5%)	0.023	2.06 (1.10-3.85)

Fatigue	0.0 (00.0%)	1 (0.5%)	1.00	2.0 (1.81-2.20)
Myalgia	40 (20.1%)	38 (19.0%)	0.802	1.07 (0.65-1.75)
Diarrhea	8 (4.0%)	2 (1.0%)	0.062	4.14(0.86-19.7)
Vomiting	0.0 (0.0%)	0 (0.0%)	A constant	

A comparison of the COVID-19 symptomatology three days after HCQ showed dramatic improvement of all symptoms with significant statistical differences except for the loss of smell. However, the same improvement was observed during the follow-up of control subjects not taking HCQ Tables 4 & 5. The results imply that no effects of HCQ on COVID-19 symptoms after three days except for sore throat) which was commoner among the control group. HCQ was not prescribed to control subjects due to their preference in 91%, anemia in 6% and morbid obesity in 3% (Figure 1).

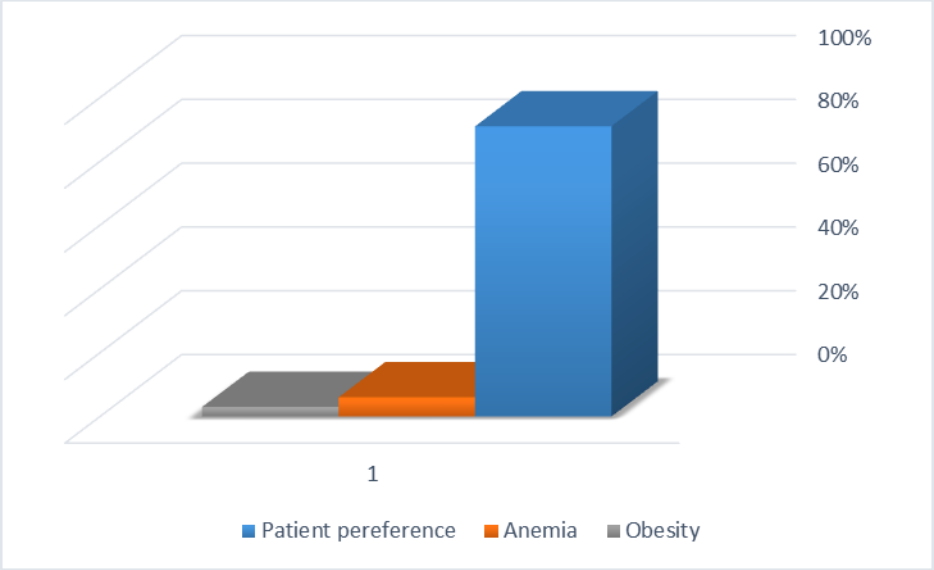

Figure 1 Reasons for not prescribing HCQ to control subjects

Table 4 A comparison of symptoms pre and post-HCQ

Character	Pre-intervention	Post-intervention	P-value	95% *CI*
Fever	101 (50.8%)	22 (11.1%)	<0.001	8.29(4.91-13.98)
Loss of smell and taste	30 (15.1%)	32 (16.1%)	0.890	0.92 (0.53-1.59)
Cough	124 (62.3%)	37 (18.6%)	<0.001	7.23 (4.57-11.44)
Sore throat	74 (37.2%)	7 (3.5%)	<0.001	16.23 (7.24-36.39)
Dyspnea	74 (37.2%)	32 (16.1%)	<0.001	3.09 (1.92-4.96)
Headache	108 (54.3%)	32 (16.1%)	<0.001	6.19 (3.87-9.90)
Fatigue	10 (5.0%)	0.0 (00.0%)	0.002	2.05 (1.85-2.27)
Myalgia	112 (56.3%)	40 (20.1%)	<0.001	5.11 (3.27-7.99)
Diarrhea	22 (11.1%)	8 (4.0%)	<0.001	2.96(1.28-6.83)
Vomiting	0.0 (0.0%)	0.0 (0.0%)	A constant	

Table 5 A comparison of symptoms control groups at baseline and three days after

Character	At baseline	Three days later	P-value	95% *CI*
Fever	102 (51.3%)	24 (12.0%)	<0.001	7.66(4.60-12.75)
Loss of smell and taste	27 (13.6%)	24 (12.0%)	0.764	1.14 (0.63-2.06)
Cough	111 (55.8%)	43 (21.5%)	<0.001	4.56 (2.95-7.09)
Sore throat	91 (45.7%)	19 (9.5%)	<0.001	8.47 (4.84-14.81)
Dyspnea	56 (28.1%)	25 (12.5%)	<0.001	2.72 (1.61-4.58)

Headache	68 (34.2%)	17 (8.5%)	<0.001	5.60 (3.14-9.97)
Fatigue	2 (1.0%)	1 (0.5%)	0.624	2.01 (.18-22.34)
Myalgia	90 (45.2%)	38 (19.0%)	<0.001	3.49 (2.23-5.48)
Diarrhea	26 (13.1%)	2 (1.0%)	<0.012	14.80(3.46-63.27)
Vomiting	0.0 (0.0%)	0 (0.0%)	A constant	

4. DISCUSSION

The present study showed no benefits of hydroxychloroquine use in the outpatient setting. The benefits observed were parts of the natural history of the disease. A study conducted in the Netherlands among hospitalized patients with COVID-19 showed no benefits HCQ in terms of mortality reduction (Peters et al., 2020). A study published in India showed no benefits of HCQ in chemoprophylaxis among health workers (Deshpande et al., 2020). A stability-controlled quasi-experiment conducted among 766 patients in a tertiary center in the United States failed to show any benefits or harms of HCQ used to treat patients with COVID-19 (Hazlett et al., 2020). Our data supported the findings of previous researchers from Brazil (Cavalcanti et al., 2020) who found no benefits of HCQ at fifteen days; the study was conducted among patients hospitalized with mild to severe COVID-19. However, the study included patients suspected of COVID-19. The study limitations were being a single-center study, so generalization cannot be insured; the small sample size is another limitation. Also, we recruited the control patients from those with contraindications or who refused HCQ. In the present study, fever, cough, and myalgia were the commonest symptoms in similarity to a study from Europe. However, loss of smell was lower, a plausible examination might be our sample presented later to the clinic (Lechien et al., 2020).

5. CONCLUSION

Hydroxychloroquine did not show any benefits in terms of COVID-19 symptomatology reduction, its use is better avoided for chemoprophylaxis and among mild disease in the outpatient setting.

Recommendations

Further larger multi-center studies focusing on the different side effects of HCQ among patients with COVID-19 especially arrhythmias are recommended

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Authors' contributions

Hyder Mirghani: Data interpretation, data analysis, and manuscript drafting
Mubarak Mohammed Theeb Alsaeed: The concept, design, data collection, and manuscript drafting
Wejdan Abdullah Hamdan Alshehri: The concept, design, data collection, and manuscript drafting
All the author revised the manuscript critically and approved it before submission

Conflicts of interest

None to declare

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Data and materials availability

All data associated with this study are present in the paper and are available upon reasonable request.

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