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Hydroxychloroquine safety outcome with an approved therapeutic protocol for COVID-19 outpatients in Saudi Arabia



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ABSTRACT

Background: Global health has been challenged by the COVID-19 pandemic since late 2019. Multiple approaches have been applied to relieve pressure on and support existing healthcare. The Saudi Arabian Ministry of Health (MOH) launched an initiative to support the national healthcare system. Since 5 June 2020, 238 outpatient fever clinics have been established nationwide. This study aimed to assess the safety outcome and reported adverse events from hydroxychloroquine use among suspected COVID-19 patients. **Methods:** The cross-sectional study included 2733 patients subjected to the MOH treatment protocol (hydroxychloroquine) and followed up for 3–7 days after initiation. Data were collected through an electronic link and cross-checked with the national database (Health Electronic Surveillance Network) and reports from the MOH Morbidity and Mortality Committee.

Results: Two hundred and forty patients (8.8%) discontinued treatment because of side effects (4.1%) and non-clinical reasons (4.7%). Adverse effects were reported among 6.7% of all participants, including mainly cardiovascular symptoms (2.5%; 0.15% with corrected QT prolongation) and gastrointestinal symptoms (2.4%). No intensive care unit admission or death was reported among these patients.

Conclusion: Our results show that hydroxychloroquine use for COVID-19 patients with mild to moderate symptoms in an outpatient setting with the recommended protocol and inclusion/exclusion criteria is safe, is highly tolerable and has minimal side effects.

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Background

COVID-19 has rapidly emerged as a pandemic viral infection that has caused significant morbidity and death worldwide. Global

healthcare systems have faced multiple challenges, ranging from the high number of patients to lack of approved therapeutic options since the outbreak of COVID-19 in late 2019. Extensive efforts have been made to explore effective therapeutic options against the virus globally (Wu et al., 2020). The World Health Organization states that there is no current evidence to recommend any specific COVID-19 treatment for patients with confirmed COVID-19 (World Health Organization, 2020).

Hydroxychloroquine has antiviral effects in vitro, and in association with azithromycin was suggested to decrease severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load in a small non-randomised study (Liu et al., 2020; Gautret et al., 2020). However, observational studies have suggested no beneficial effect of chloroquine or hydroxychloroquine in hospitalised patients with COVID-19 (Geleris et al., 2020; Rosenberg et al., 2020).

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The Saudi Arabian Ministry of Health (MOH) has launched an initiative to support the national healthcare system. Since 5 June 2020, 238 outpatient fever clinics have been established across Saudi Arabia under the direct supervision of the Primary Healthcare Deputyship at the MOH. The target population for these clinics was suspected COVID-19 patients showing mild to moderate symptoms (on the basis of the MOH protocol) (Anon, 2020), and the implemented protocol was based on hydroxychloroquine with zinc sulphate as the recommended treatment of choice.

Given the hydroxychloroquine safety profile, multiple exclusion criteria and several recommendations for patient safety were added to the protocol. Baseline ECG and electrolyte results were requested before initiation to overcome and follow up the risk of cardiac arrhythmias leading to sudden death (if they occurred) in addition to a follow-up ECG and an electrolyte test within 3–7 days of therapy initiation. On the other hand, patients at high risk of developing side effects, especially cardiac side effects, were excluded from hydroxychloroquine use and were advised to follow standard supportive care.

Evidence regarding the potential effect and safety of hydroxychloroquine therapy, whether given alone or in combination with zinc sulphate, for COVID-19 patients is not clear and is limited. In addition, several reports raised concerns about hydroxychloroquine safety. Therefore, this study aimed to assess the safety outcomes and reported adverse events among COVID-19 patients attending outpatient fever clinics and subjected to the MOH-approved treatment protocol within 3–7 days in Saudi Arabia. This publication is part of a national project to assess the safety outcomes from the national fever clinic initiative in Saudi Arabia.

Objectives

The objectives were to determine the reported adverse events among suspected COVID-19 patients subjected to the MOH-approved treatment protocol and assessed within 3–7 days, including the development of treatment-related adverse effects, medication tolerability, hospitalisation, intensive care unit (ICU) admission and death.

Methods

Study design and setting

A cross-sectional study was conducted from 5 June 2020 to the 7 July 2020 in 238 outpatient fever clinics in Saudi Arabia.

Study participants

The sample size included 2733 eligible suspected COVID-19 patients subjected to the MOH treatment protocol before the

PCR results were received. Of 60,738 consecutive suspected COVID-19 patients who attended clinics during the study period, 23,043 eligible patients (37.9%) were given the approved treatment protocol. Of these, 2733 patients who revisited the clinics within 3–7 days and fulfilled the inclusion criteria were included in the sample and reassessed for adverse events and the safety outcome of the approved treatment protocol. Mild to moderate cases were defined on the basis of the MOH protocol as patients with symptoms (no oxygen requirements/no evidence of pneumonia but with other symptoms of COVID-19, e.g. fever) (Anon, 2020).

The study included patients aged 19 years or older presenting with subjective fever (temperature higher than 38 °C) and with one or more COVID-19 symptoms, including sore throat, cough, diarrhoea, shortness of breath, headache and myalgia, and those who revisited the clinics within 3–7 days. The study excluded morbidly obese patients, pregnant and lactating women, those with glucose 6-phosphate dehydrogenase deficiency and patients with known cardiac-related issues. The study did not exclude other co-morbidities.

Study tools

Data from patient health records were entered into pre-designed advanced online forms by data entry officers on the first visit of the patient to the clinic at the local Medical Affairs. The data were collected through an electronic link and cross-checked with the national health electronic surveillance network database and reports from the MOH Morbidity and Mortality Committee. All collected data were sent to the district Medical Affairs for follow-up and investigation to determine the safety outcome of the treatment protocol during the first 3–7 days, including medication discontinuation, reported adverse drug reactions, especially gastrointestinal (GI) symptoms and ECG abnormalities (by the treating physician), complete recovery from COVID-19 symptoms, hospitalisation, ICU admission and death. ECG changes were defined as corrected QT (QTc) prolongation (greater than 470 ms or an increase of more than 40 ms from the baseline), non-specific changes such as sinus tachycardia or T wave inversion.

A standardised prescription form was written and distributed with the written treatment protocol. The prescription listed hydroxychloroquine for a total duration of 5 days, starting with 400 mg twice on day 1, followed by 200 mg twice daily for the remaining 4 days. No dose adjustment was recommended for patients with renal or hepatic impairment. The prescription also included zinc sulphate, 60 mg orally once daily for 5 days, paracetamol and an antihistamine. The prescription did not include azithromycin.

Table 1
Socio-demographic characteristics among both PCR-positive and PCR-negative participants (n = 2733).

		PCR positive (n = 1555)		PCR negative/NA (n = 1178)		Total (n = 2733)	
		No.	%	No.	%	No.	%
Sex	Male	1079	69.4	846	71.8	1925	70.4
	Female	476	30.6	332	28.2	808	29.6
Age (years)	19–30	447	28.7	372	31.6	819	30.0
	31–40	567	36.5	426	36.2	993	36.3
	41–50	320	20.6	243	20.6	563	20.6
	51–64	215	13.8	135	11.5	350	12.8
	≥65	6	0.4	2	0.2	8	0.3
Discontinuation of treatment	Yes	143	9.2	97	8.2	240	8.8
	No	1412	90.8	1081	91.8	2493	91.2
Medication side effects	Yes	100	6.4	83	7.0	183	6.7
	No	1455	93.6	1095	93.0	2550	93.3

NA, not available.

Statistical analysis

The outcome variables included reported adverse events and the safety outcome of the treatment protocol used, including the percentages of patients hospitalised, admitted to the ICU, who died, who discontinued medication and who developed side effects (e.g., ECG changes compared with baseline and GI symptoms). All data were analysed with IBM SPSS Statistics version 21.

Ethical considerations

This research was approved and followed closely by the MOH Institutional Review Board. Informed consent was obtained, by the treating physician, from the participants after explanation of the study. Those who refused to participate in the study were excluded and continued with standard supportive care. All information collected will be kept confidential and will not be used for purposes other than the study. Hydroxychloroquine therapy was discontinued at any time in patients who reported any possible medication-related adverse events. Unstable patients at presentation or those who showed clinical progression/deterioration on days 3–7 were referred to the hospital and continuously followed up by the research team for outcomes.

Results

Table 1 presents the socio-demographic characteristics of the participants. Of the 2733 patients, 56.89% were PCR positive, and the remaining were PCR negative or their results were not obtained. Most of them were men (69.4% and 71.8% in the two groups, respectively). More than one third (36.3%) of the patients studied were aged 31–40 years, and 20.6% were 41–50 years old. When the patients were reassessed within 3–7 days, 183 patients (6.7%) had experienced medication adverse effects and 240 patients (8.8%) had discontinued the treatment protocol.

Of the 240 patients who discontinued the treatment protocol, 112 patients (46.7%, 4.1% of the total) experienced medication adverse effects, and the remaining 128 patients (53.3%, 4.6% of the total) discontinued the treatment protocol for non-clinical reasons not related to medication adverse effects (Table 2). One of the most common non-clinical reasons was the patient was unwilling or unconvinced to continue therapy.

Of the 183 patients (6.7% of the total) who experienced medication adverse effects, 112 (61.2%, 4.1% of the total) discontinued the treatment protocol, and the remaining 71 patients (38.8%, 2.6% of the total) continued the treatment irrespective of adverse effects (Table 3).

Table 4 gives the frequency of the reported medication adverse effects among the participants. The most common reported adverse effect was a cardiovascular adverse event (69 patients, 37.7%, 2.5% of the total), which included palpitation, chest pain and ECG changes. Cardiovascular symptoms reported included subjective palpitation, chest pain and shortness of breath without sequelae or adverse clinical outcomes (65 patients, 35.9%, 2.4% of the total); non-specific ECG changes other than QTc prolongation were included in this group. QTc prolongation greater than 470 ms or an increase of more than 40 ms from the baseline was reported

Table 2

Frequency of medication side effects among patients who discontinued the treatment protocol ($n = 240$).

	No.	Frequency (%)
Medication side effects	112	46.7
No medication side effects	128	53.3

Table 3

Frequency of discontinuation of the approved treatment protocol among patients who developed side effects ($n = 183$).

	No.	Frequency (%)
Discontinued treatment	112	61.2
Continued treatment	71	38.8

in four patients only (2.2%, 0.15% of the total); of the four patients, two had QTc prolongation (492 ms and 507 ms). The second most common adverse effect was GI symptoms, including nausea, vomiting, abdominal pain and diarrhoea.

In all reported cases with medication adverse effects, no ICU admission or death was reported in patients who received hydroxychloroquine. The final reported adverse events will be revised with the final project analysis.

Discussion

The study included 2733 eligible patients who were subjected to the MOH treatment protocol and revisited the clinics between 3 and 7 days after initiation of therapy. Most of them were men (70.4%) in the 19–30-year and 31–40-year age groups (30.0% and 36.3%, respectively). On reassessment of the participants within 3–7 days, 240 patients (8.8%) discontinued the treatment protocol because of the development of side effects (46.7%) and for other non-clinical reasons not related to medication side effects (53.7%).

Hooks et al. (2020) studied the effects of hydroxychloroquine treatment on QTc interval among 734 patients (mean age 64.0 years \pm 10.9 years), of whom 90% were men. They recorded an increase in QTc interval from 424.4 \pm 29.7 ms to 432.0 \pm 32.3 ms ($P < 0.0001$) during hydroxychloroquine treatment, and found that chronic kidney disease, a history of atrial fibrillation and heart failure were independent risk factors for QTc prolongation. A more frequent prolongation of the QTc interval among patients receiving hydroxychloroquine alone or with azithromycin than in those who were not receiving either agent was documented by Cavalcanti et al. (2020) and Lagier et al. (2020) (among 0.67% of patients).

The current study recorded medication adverse effects (6.7%) among all participants studied, including mainly cardiovascular symptoms (37.7%, 2.5% of the total), for example palpitation, chest pain and ECG changes followed by GI symptoms (e.g., nausea, vomiting, abdominal pain and diarrhoea). Among those who developed adverse effects, 61.2% (4.1% of the total) discontinued the treatment protocol. Although cardiovascular symptoms were reported by patients during the treatment course, we cannot exclude the effect of COVID-19 overall symptoms overlapping with patient-reported adverse effects.

A higher percentage of adverse events was reported by Tang et al. (2020) among patients who received hydroxychloroquine (30%) compared with patients who did not receive hydroxychloroquine (9%), with patients reporting serious adverse events, the most common being diarrhoea, reported in 7 of 70 patients (10%). Similarly, Lofgren et al. (2020) reported a higher frequency of adverse effects (84%) and medication adverse effects (27%) among hydroxychloroquine recipients, mainly upset stomach or nausea (25% with daily administration, 18% with twice weekly administration and 16% with weekly administration versus 10% for placebo), followed by diarrhoea, vomiting or abdominal pain (23% with daily administration, 16% with twice weekly administration and 12% with weekly administration versus 6% for placebo). These findings are inconsistent with those of Satlini et al. (2020), who found that patients with incident vomiting or diarrhoea were rare.

Other adverse events were recorded in a meta-analysis by Eljaalya et al. (2020), who investigated the pooled adverse effects

Table 4
Frequency of reported side effects among the participants.

	PCR-positive patients (n = 100)		Patients who developed side effects (n = 183)		All patients who revisited the clinic on days 3–7 (n = 2733)
	No.	%	No.	%	
Cardiovascular symptoms (palpitation, chest pain and ECG changes ^{a,b})	45	45	69	37.7	2.5
GI symptoms (nausea, vomiting, abdominal pain and diarrhoea)	27	27	65	35.5	2.4
Cardiovascular symptoms and GI symptoms	3	3	5	2.7	0.2
Itching/medication hypersensitivity	2	2	6	3.3	0.2
Visual complication	3	3	3	1.6	0.1
Dizziness	0	0	2	1.1	0.07
Electrolyte abnormalities compared with the baseline ^c	1	1	2	1.1	0.07
Other symptoms (less commonly reported) ^d	19	19	31	16.9	1.1
Total	100	100	183	100.0	6.6

GI, gastrointestinal.

^a ECG changes: changes in ECG reading compared with the baseline, corrected QT prolongation, sinus tachycardia and non-specific T wave changes.

^b Corrected QT prolongation (greater than 470 ms or an increase of more than 40 ms from the baseline) was reported in four patients.

^c Electrolyte abnormality: hypomagnesaemia or hypokalaemia.

^d Symptoms reported by the patients not directly related to hydroxychloroquine (e.g. low back pain, fatigue and muscle pain).

of hydroxychloroquine among nine randomised trials in 916 patients and found that hydroxychloroquine caused significantly more skin pigmentation than placebo (Peto odds ratio (OR), 4.64; 95% confidence interval (CI), 1.13–19.00; $P = 0.033$; $I^2 = 0\%$), while they found other adverse events were not statistically significant: rash (Peto OR, 1.11; 95% CI, 0.3–3.77; $P = 0.03$; $I^2 = 0\%$); GI adverse events (Peto OR, 1.43; 95% CI, 0.55–3.72; $P = 0.46$; $I^2 = 15.17\%$); headache (Peto OR, 1.94; 95% CI, 0.65–5.78; $P = 0.23$; $I^2 = 9.99\%$); dizziness (Peto OR, 1.32; 95% CI, 0.49–3.52; $P = 0.58$; $I^2 = 0\%$); fatigue (Peto OR, 2.13; 95% CI, 0.76–5.98; $P = 0.15$; $I^2 = 0\%$); and visual adverse events (Peto OR, 1.61; 95% CI, 0.76–3.41; $P = 0.22$; $I^2 = 0\%$). Inconsistent with our study, cardiac toxicity was not reported.

The current study recorded no ICU admission or death among the participants related to hydroxychloroquine use. Lagier et al. (2020) reported a case fatality rate of 0.9% but they noticed a decreased risk of ICU admission and death (hazard ratio, 0.18; 95% CI, 0.11–0.27) and decreased risk of hospitalisation for 10 days or more (OR, 0.38; 95% CI, 0.27–0.54) among patients treated with the hydroxychloroquine–azithromycin combination. In our study, the low incidence of side effects might be related to the dosing regimen selected (400 mg twice daily for 1 day followed by 200 mg twice daily) compared with other randomised controlled trials. The trial by Skipper et al. (2020), which used 800 mg once, followed by 600 mg in 6–8 h and then 600 mg daily for the next 4 days, showed a higher incidence of side effects in the hydroxychloroquine arm (43%) versus the placebo arm (22%).

The present study recorded 8.8% discontinuation of hydroxychloroquine use among participants due to the development of adverse effects (46.7%, 4.1% of the total) and for non-clinical reasons (53.3%, 4.6% of the total), which was consistent with the findings of Satlini et al. (2020), who found that 89% of their patients completed the hydroxychloroquine course. Only three patients discontinued therapy because of QTc prolongation.

Of 23,043 patients who received hydroxychloroquine and did not revisit the clinic on days 3–7, variables of safety measures were not obtained in this population. Nevertheless, the data regarding hospitalisation and death were cross-matched with the data from the national Morbidity and Mortality Committee and regional Medical Affairs across Saudi Arabia, and there was no reported hospitalisation or death regarding hydroxychloroquine adverse effects.

Conclusion

Overall, the results show that hydroxychloroquine was tolerable in our patients and with minimal reported adverse effects. In addition, death and hospitalisation directly related to

hydroxychloroquine treatment were not reported. Thus, our results provide assurance that the use of hydroxychloroquine for COVID-19 patients with mild to moderate symptoms in the outpatient setting with the recommended protocol and inclusion/exclusion criteria is safe, is highly tolerable and has minimal side effects.

Conflict of interest

None declared.

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This research was conducted under the umbrella of the Saudi Arabian Ministry of Health and did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Ethics approvals

This research was approved and followed closely by the Ministry of Health Institutional Review Board (log number 20-129M). Informed consent was obtained, by the treating physician, from the participants after explanation of the study. Those who refused to participate in the study were excluded and continued with standard supportive care. All information collected was kept confidential and will not be used for purposes other than the study.

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